CHAPTER 14

Retinal Vascular Disease

Diabetic retinopathy

Systemic considerations

Diabetes mellitus is a common metabolic disorder characterized by sustained hyperglycaemia of variable severity, secondary to lack, diminished efficacy, or both of endogenous insulin. Diabetes may be insulin-dependent (IDDM) or non-insulin-dependent (NIDDM), perhaps more accurately termed type 1 and type 2 diabetes respectively (*see* Chapter 20). Diabetic retinopathy (DR) is commoner in type 1 (40%) than in type 2 diabetes mellitus (20%), and is the most common cause of legal blindness between the ages of 20 and 65 years.

Risk factors

1. **Duration of diabetes** is the most important. In patients diagnosed with diabetes before the age of 30 years, the incidence of DR after 10 years is 50% and after 30 years 90%. DR rarely develops within 5 years of the onset of diabetes or before puberty, but about 5% of type 2 diabetics have DR at presentation.
2. **Poor metabolic control** is less important than duration, but is nevertheless relevant to the development and progression of DR.
3. **Pregnancy** is occasionally associated with rapid progression of DR. Predicating factors include poor pre-pregnancy control of diabetes, too rapid tightening of control during the early stages of pregnancy and the development of pre-eclampsia and fluid imbalance.
4. **Hypertension**, if poorly controlled, is associated with worsening of DR and the development of proliferative diabetic retinopathy (PDR) in both type 1 and type 2 diabetics.
5. **Nephropathy**, if severe, is associated with worsening of DR. Conversely, treatment of renal disease (e.g. renal transplantation) may be associated with improvement of retinopathy and a better response to photocoagulation.
6. **Other** risk factors include smoking, obesity and hyperlipidaemia.

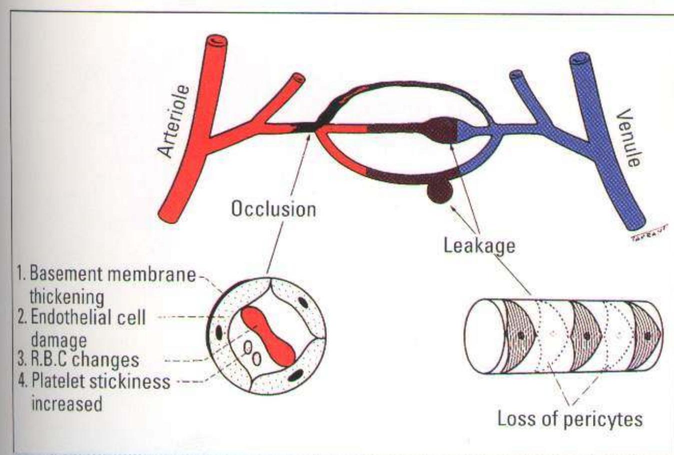


Fig. 14.1
Pathogenesis of diabetic retinopathy

Benefits of intensive metabolic control

- It delays the onset of DR, although it does not prevent it.
- It slows the progression of background diabetic retinopathy (BDR).
- It decreases the rate of conversion of pre-proliferative retinopathy (PPDR) to PDR.
- It decreases the incidence of macular oedema.
- It decreases the need for laser photocoagulation.

Pathogenesis

DR is a microangiopathy primarily affecting the pre-capillary arterioles, capillaries and post-capillary venules, although larger vessels may also be involved. Retinopathy exhibits features of both microvascular occlusion and leakage. Clinically, DR may be: (a) *background (non-proliferative)* in which the pathology remains intraretinal, (b) *proliferative* in which the pathology extends onto or beyond the retinal surface and (c) *pre-proliferative*, which has features of imminent proliferative disease.

Microvascular occlusion

1. **Pathogenesis** (Fig. 14.1)
   a. ***Capillary*** changes consist of loss of pericytes, thickening of the basement membrane and damage and proliferation of endothelial cells. Figure 14.2 shows a normal capillary bed and Figure 14.3 the capillary bed in a diabetic fundus.
   b. ***Haematological*** changes consist of deformation and increased rouleaux formation of red blood cells and increased platelet stickiness and aggregation, leading to decreased oxygen transport.
2. **The consequence** of retinal capillary non-perfusion is retinal ischaemia, which initially develops in the mid-retinal periphery. The two main effects of retinal hypoxia are the following (Fig. 14.4):

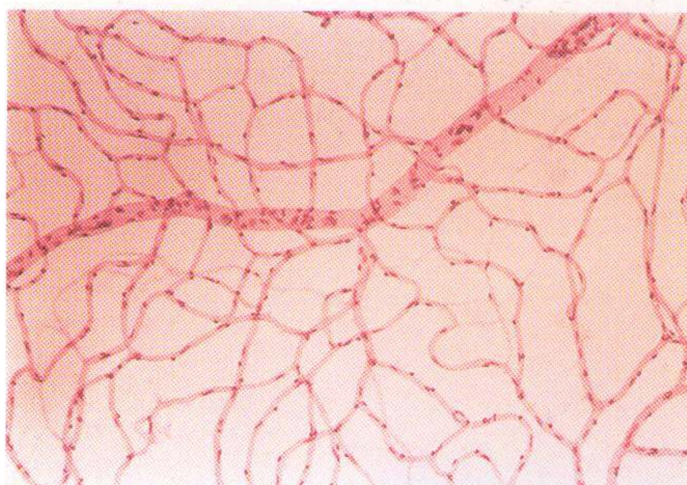


Fig. 14.2
Normal retinal capillary bed showing equal distribution between pericytes with round dark stained nuclei and endothelial cells with elongated pale staining cells

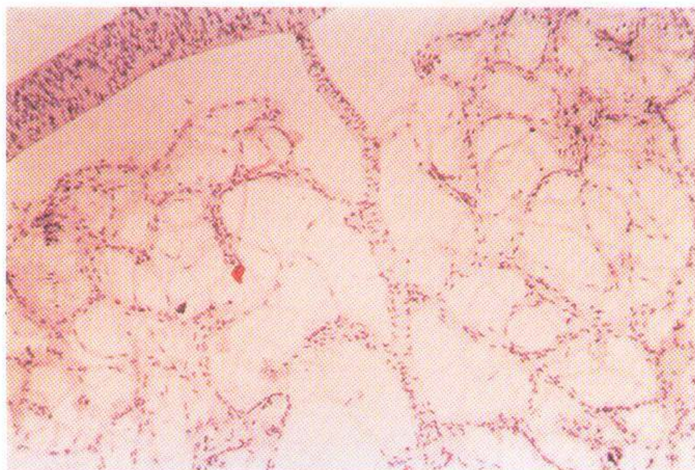


Fig. 14.3
Diabetic retinal capillary bed with many acellular capillaries due to occlusion; remaining capillaries are dilated and show loss of pericytes and an increased number of endothelial cells

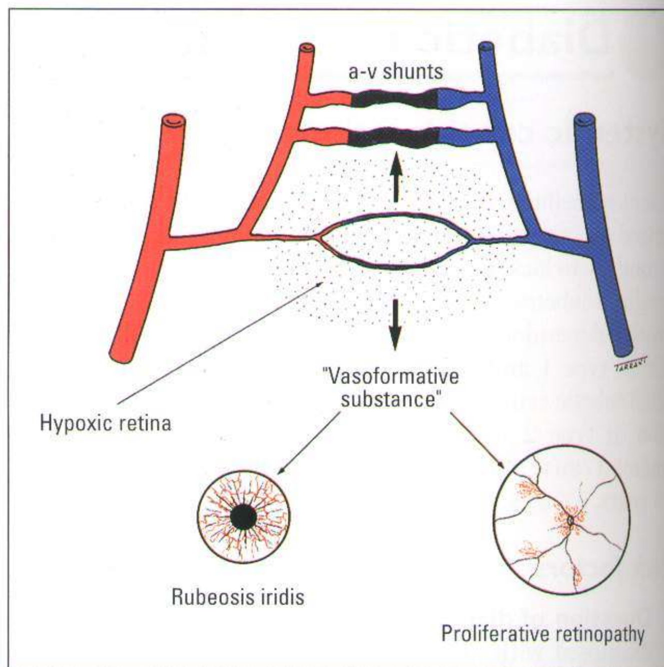


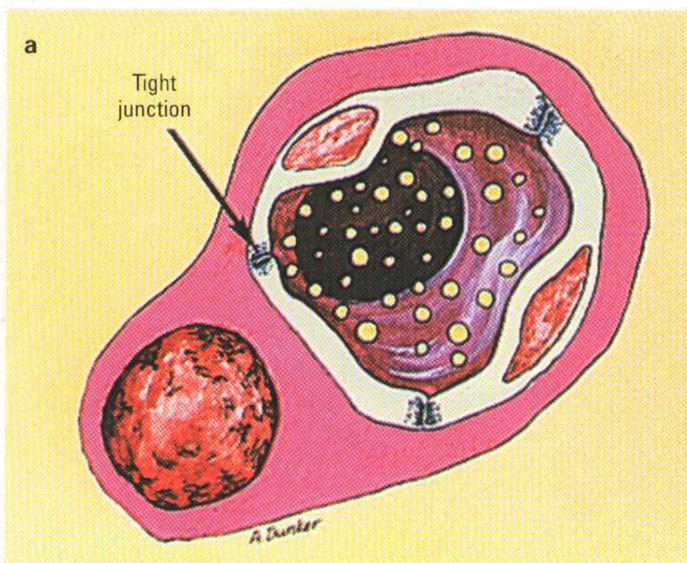
Fig. 14.4
Consequences of retinal ischaemia in diabetic retinopathy

*a. **Arteriovenous shunts*** associated with significant capillary occlusion ('drop-out') run from arterioles to venules. As it is unclear whether these lesions represent new vessels or opening of pre-existing vascular channels, they are often referred to as 'intraretinal microvascular abnormalities' (IRMA).

*b. **Neovascularization*** is thought to be caused by 'vasoformative substances' (growth factors) elaborated by hypoxic retinal tissue in an attempt to revascularize hypoxic retina. These substances promote neovascularization on the retina and optic nerve head (PDR) and occasionally on the iris (rubeosis iridis). Many growth factors have been identified; vascular endothelial growth factor (VEGF) appears to be of particular importance.

Microvascular leakage

1. **Pathogenesis**. Breakdown of the inner blood–retinal barrier leads to leakage of plasma constituents into the retina (Fig. 14.5b). Physical weakening of the capillary walls results in localized saccular outpouchings of the vessel wall, termed microaneurysms, which may leak or become thrombosed.
2. **Consequences** of increased vascular permeability include the development of intraretinal haemorrhages and oedema which may be diffuse or localized (Fig. 14.6).
   *a. **Diffuse retinal oedema*** is caused by extensive capillary dilatation and leakage.



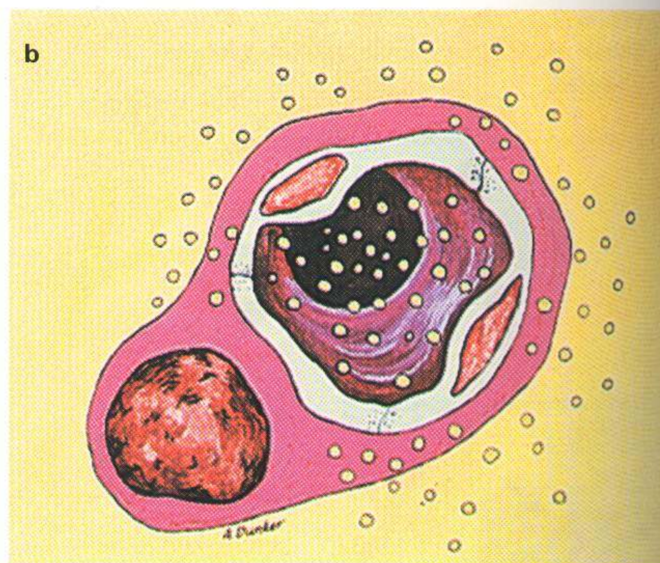


Fig. 14.5
(**a**) Tight junctions of endothelial cells forming the inner blood–retinal barrier; (**b**) leakage due to disruption of the inner blood–retinal barrier in diabetic retinopathy (Courtesy of Wilmer Institute)

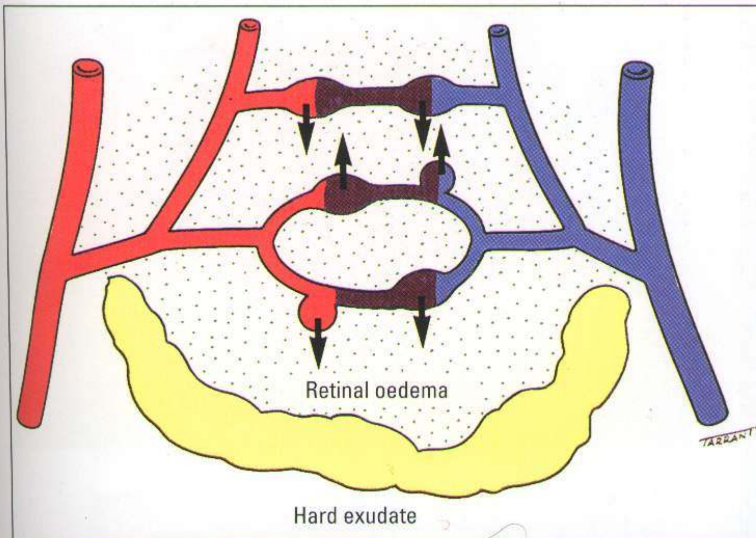
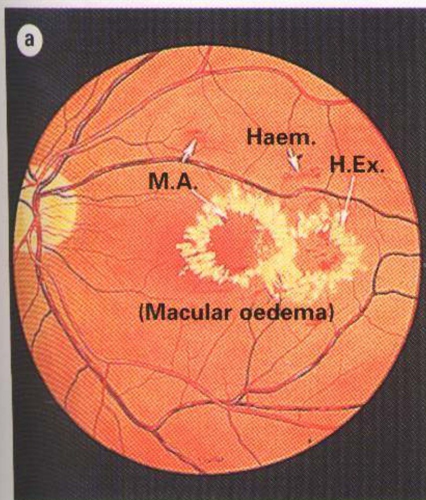


Fig. 14.6
Consequences of increased vascular permeability in diabetic retinopathy



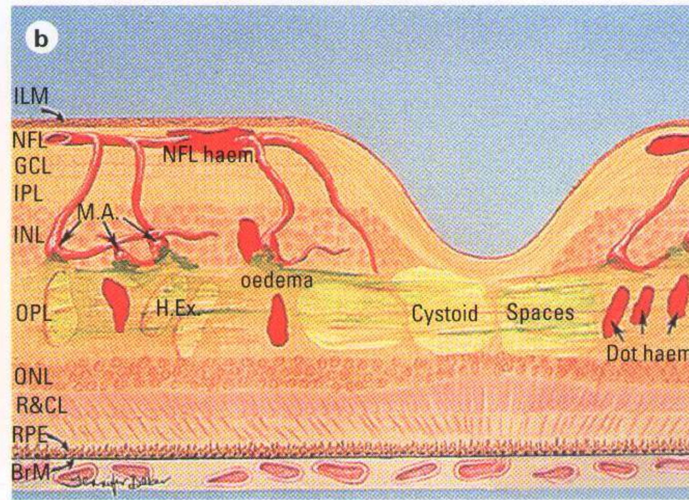


Fig. 14.7
Background diabetic retinopathy;
(**a**) clinical features;
(**b**) location of lesions
(Courtesy of Wilmer Institute)

b. Localized retinal oedema is caused by focal leakage from microaneurysms and dilated capillary segments. Chronic localized retinal oedema leads to the deposition of 'hard exudates' at the junction of normal and oedematous retina. These exudates, composed of lipoprotein and lipid-filled macrophages, typically surround leaking microvascular lesions in a circinate pattern. When leakage ceases, they absorb spontaneously over a period of months or years, either into the healthy surrounding capillaries or by phagocytosis of their lipid content. Chronic leakage leads to enlargement of the exudates and the deposition of cholesterol.

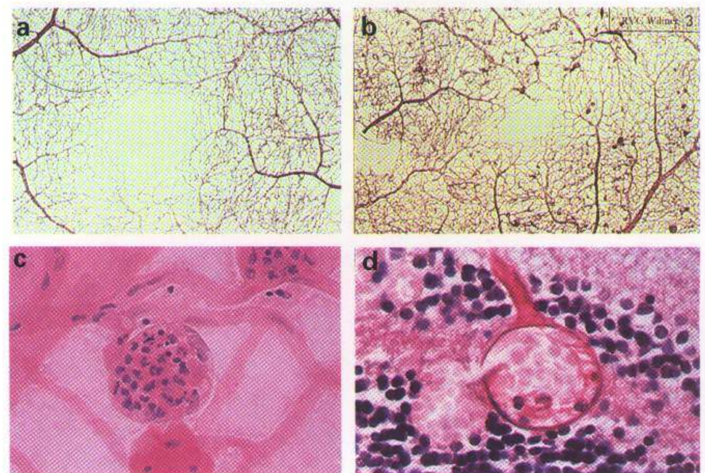


Fig. 14.8
(**a**) Trypsin digest of normal retina; (**b**) trypsin digest of diabetic retina showing perifoveal microaneurysms; (**c**) high power view showing a microaneurysm containing many cells; (**d**) cross-section of a microaneurysm (Courtesy of Wilmer Institute)

Background diabetic retinopathy

Clinical features

Figure 14.7a shows the clinical features of background DR and Figure 14.7b the location of the lesions within the retina.

1. Microaneurysms (Fig. 14.8) are located in the inner nuclear layer and are the earliest clinically detectable lesions.

a. Signs. Tiny, round, red dots, initially appearing temporal to the fovea (Fig. 14.9). When coated with blood they may be indistinguishable from dot haemorrhages.

b. FA shows tiny hyperfluorescent dots, representing non-thrombosed microaneurysms, typically in greater

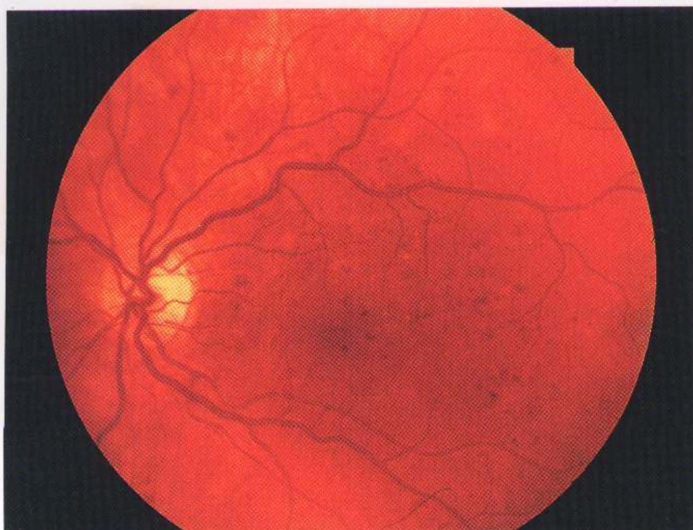


Fig. 14.9
Microaneurysms and dot haemorrhages in early background diabetic retinopathy

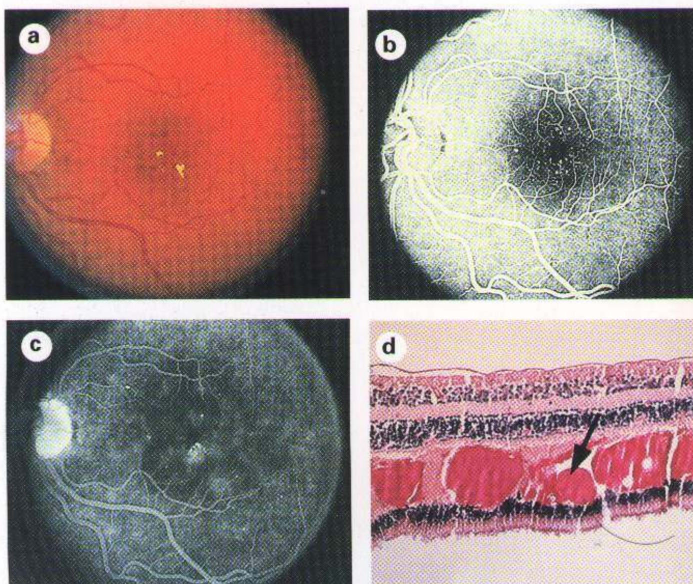


Fig. 14.10
Background diabetic retinopathy. **(a)** Hard exudates; **(b)** early FA showing microaneurysms; **(c)** late FA showing leakage; **(d)** hard exudate in the outer plexiform layer (Courtesy of Wilmer Institute)

numbers than that visible ophthalmoscopically (Fig. 14.10b). Late frames show diffuse hyperfluorescence due to leakage (Fig. 14.10c).

2. **Hard exudates** lie within the outer plexiform layer (Fig. 14.10d).
   a. ***Signs***. Waxy, yellow lesions with relatively distinct margins (Fig. 14.10a) often arranged in clumps and/or rings at the posterior pole (Fig. 14.11). A ring of hard exudates (circinate exudate) often exhibits microaneurysms at its centre. With time, number and size tend to increase, and the fovea may be threatened or involved (Fig. 14.12).
   b. ***FA*** shows hypofluorescence due to blockage of background choroidal fluorescence.
3. **Retinal oedema** is initially located between the outer plexiform and inner nuclear layers. Later it may also involve the inner plexiform and nerve fibre layers, until eventually the entire thickness of the retina becomes oedematous. With further accumulation of fluid the fovea assumes a cystoid appearance (cystoid macular oedema) (*see* Fig. 13.82).
   a. ***Signs***. Retinal thickening is best detected by slit-lamp biomicroscopy with a Goldmann lens.
   b. ***FA*** shows diffuse late hyperfluorescence due to retinal capillary leakage (*see* Fig. 14.10c).
4. **Haemorrhages**
   a. ***Intraretinal*** haemorrhages arise from the venous end of capillaries and are located in the compact middle layers of the retina with a resultant red, 'dot-blot' configuration (*see* Fig. 14.11).
   b. ***Retinal nerve fibre layer*** haemorrhages arise from the larger superficial pre-capillary arterioles and are therefore flame-shaped.

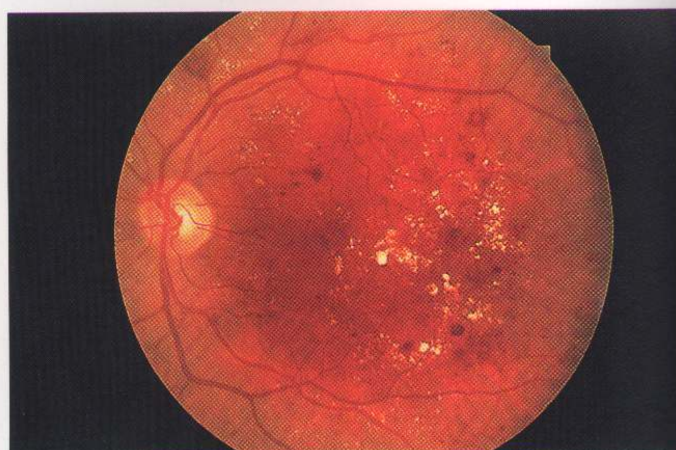


Fig. 14.11
Severe background diabetic retinopathy with circinate exudates and haemorrhages

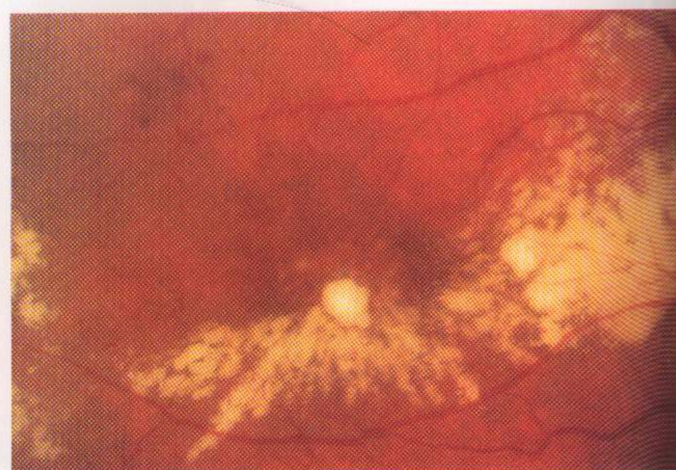


Fig. 14.12
Hard exudates at the macula in background diabetic retinopathy

Management

Patients with mild BDR require no treatment but should be reviewed annually. Apart from optimal control of diabetes,

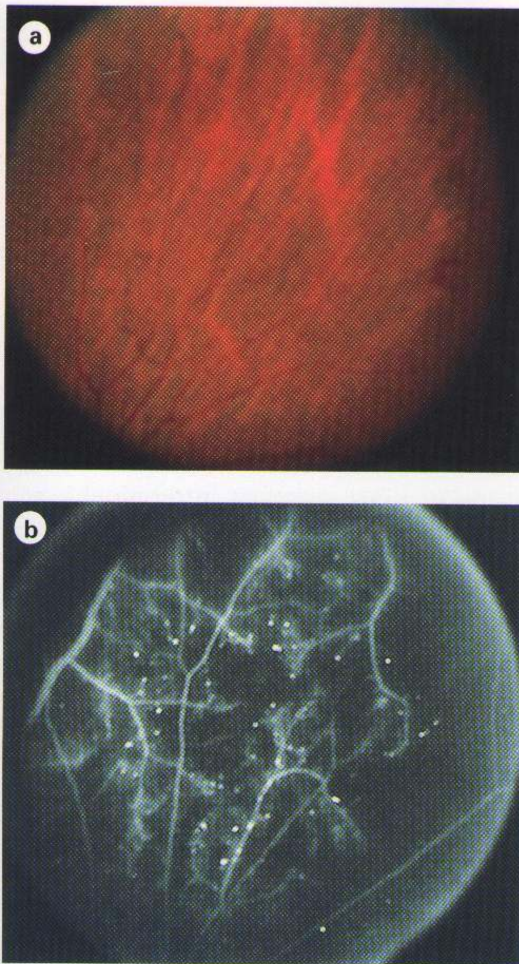


Fig. 14.13
(**a**) Peripheral retinal ischaemia; (**b**) FA showing capillary non-perfusion (Courtesy of Wilmer Institute)

associated factors such as hypertension, anaemia or renal failure should also be addressed.

Preproliferative diabetic retinopathy

BDR that exhibits signs of imminent proliferative disease is termed preproliferative diabetic retinopathy (PPDR). The clinical signs of PPDR indicate progressive retinal ischaemia, seen on FA as extensive hypofluorescent areas of retinal non-perfusion (capillary drop-out) (Fig. 14.13b). Figure 14.14a shows the clinical features of PPDR and Figure 14.14b the location of the lesions. The risk of progression to proliferative disease appears proportional to the number of lesions.

Clinical features

1. Cotton wool spots represent focal infarcts of the retinal nerve fibre layer, due to occlusion of pre-capillary arterioles (Fig. 14.15c and d). Interruption of axoplasmic transport with subsequent build-up of transported material within the axons (axoplasmic stasis) are responsible for the white appearance of the lesions.

a. Signs. Small, whitish, fluffy superficial lesions which obscure underlying blood vessels and are clinically

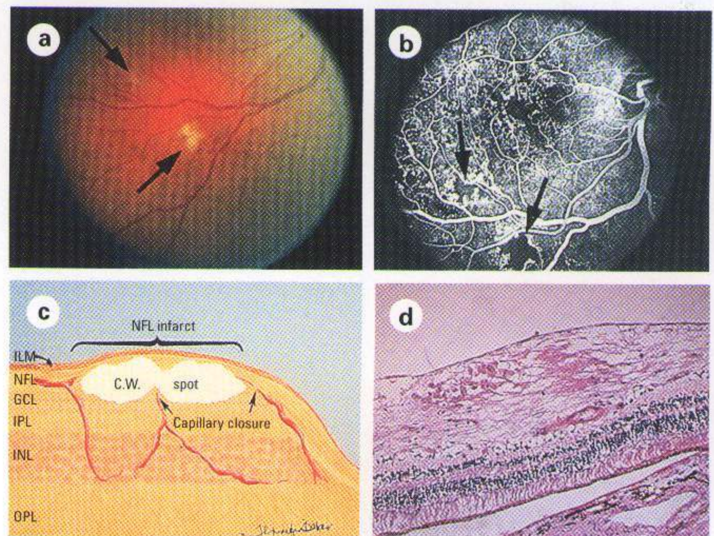
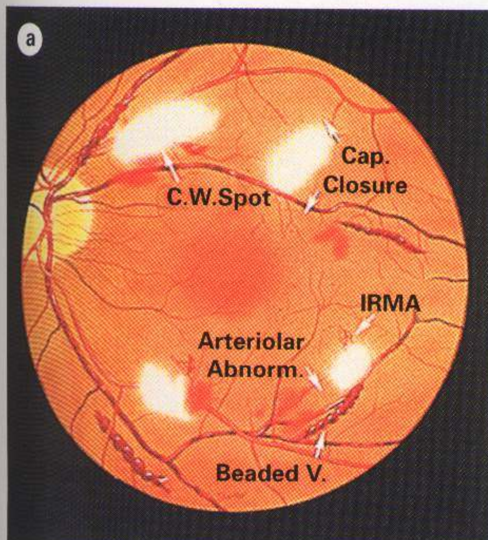


Fig. 14.15
(**a**) Cotton wool spots; (**b**) FA showing hypofluorescence due to blockage by the cotton wool spots and small adjacent areas of capillary non-perfusion; (**c**) cotton wool spot adjacent to an area of capillary closure; (**d**) low-power photomicrograph showing infarction and disorganization of the retinal nerve fibre layer and ganglion cell layer following capillary closure (Courtesy of Wilmer Institute)



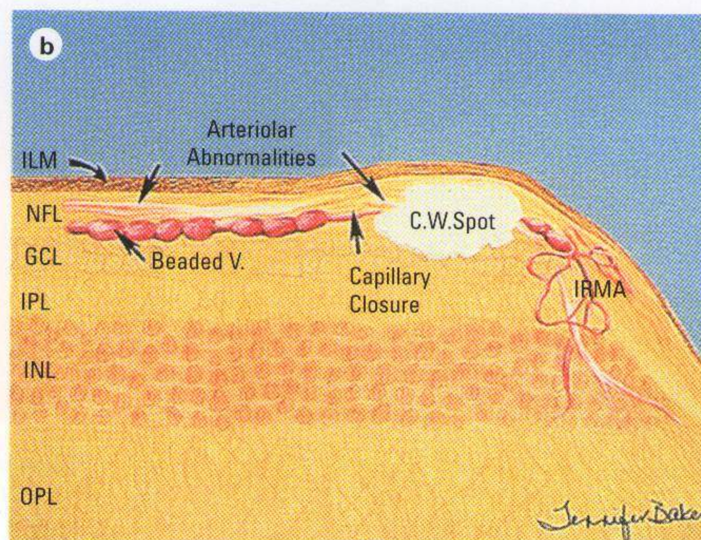


Fig. 14.14
Preproliferative diabetic retinopathy; (**a**) clinical features; (**b**) location of lesions (see *text*) (Courtesy of Wilmer Institute)

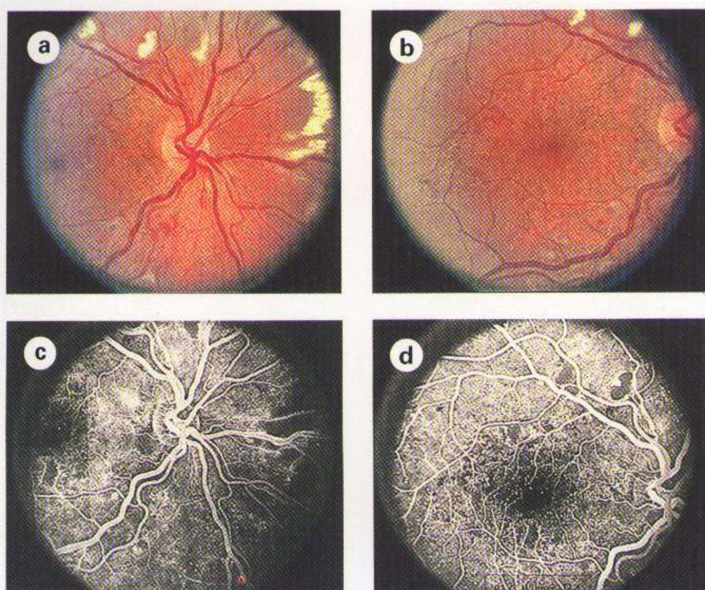


Fig. 14.16
(**a** and **b**) Cotton wool spots and venous dilatation; (**c** and **d**) FA showing spotty hyperfluorescence of microaneurysms and areas of hypofluorescence due to capillary non-perfusion (Courtesy of Wilmer Institute)

evident only in the post-equatorial retina, where the nerve fibre layer is of sufficient thickness to render them visible (Figs 14.15a, and 14.16a and b).

b. FA shows focal hypofluorescence due to blockage of background choroidal fluorescence frequently associated with adjacent capillary non-perfusion (Figs 14.15b, and 14.16c and d).

2. Intraretinal microvascular abnormalities (IRMA) represent shunts that run from retinal arterioles to venules, thus by-passing the capillary bed, and are therefore often seen adjacent to areas of capillary closure (Fig. 14.17a).

a. Signs. Fine red lines that run from arterioles to venules, thus resembling focal areas of flat retinal new vessels (Figs 14.17b and 14.18a). The main distinguishing features of IRMA are their intraretinal location, their failure to cross major retinal blood vessels and absence of leakage on FA.

b. FA shows focal hyperfluorescence associated with adjacent areas of capillary closure (Fig. 14.18b).

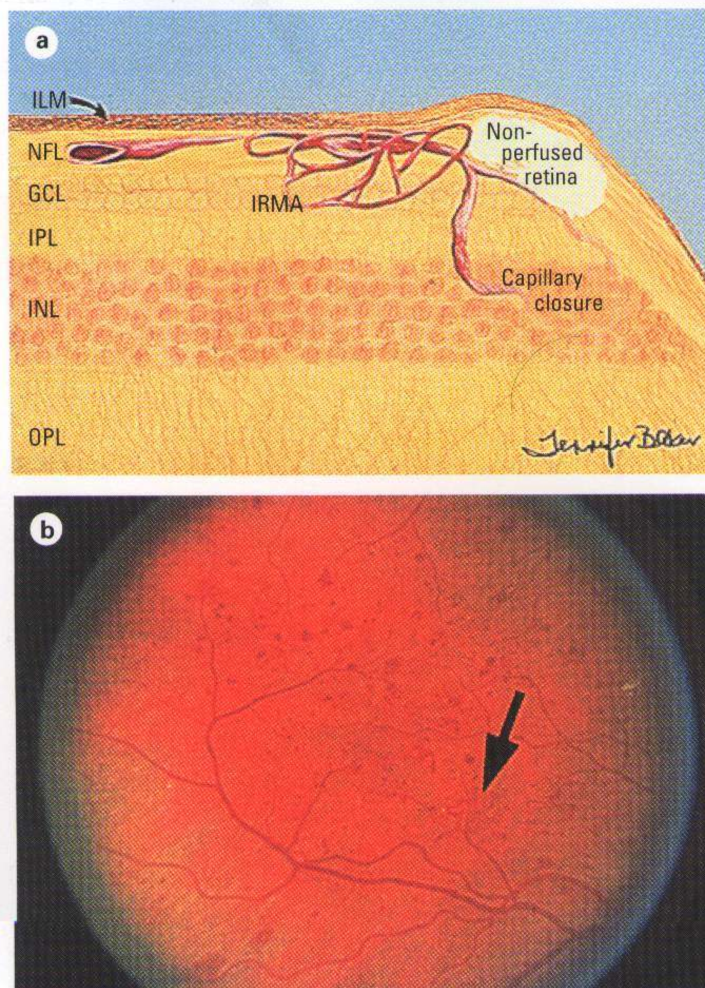


Fig. 14.17
Intraretinal microvascular abnormalities. (**a**) Location in the superficial retina adjacent to areas of non-perfusion; (**b**) clinical appearance (Courtesy of Wilmer Institute)

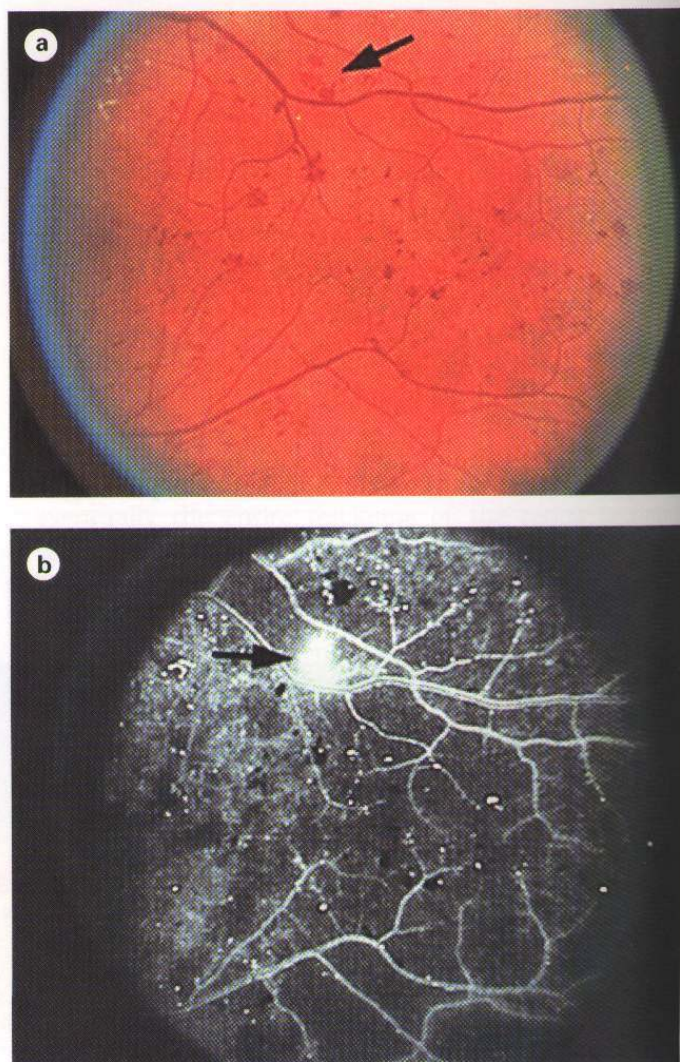


Fig. 14.18
(**a**) Intraretinal microvascular abnormalities; (**b**) FA showing focal hyperfluorescence and extensive capillary non-perfusion (Courtesy of Wilmer Institute)



Fig. 14.19
Venous looping

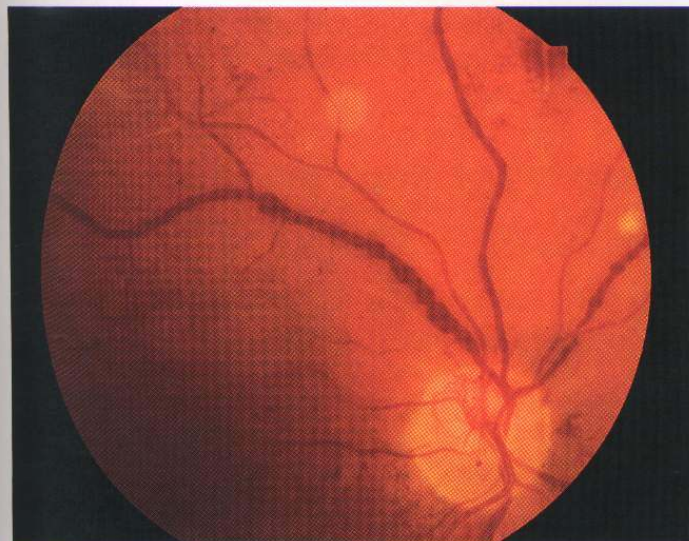


Fig. 14.20
Venous beading and mild disc new vessels

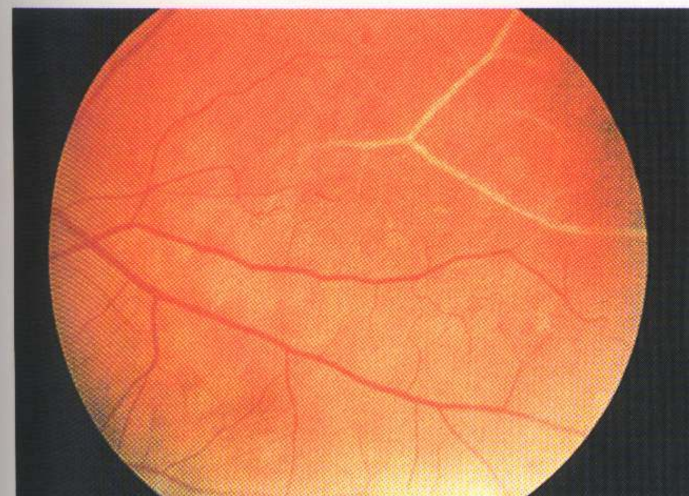


Fig. 14.21
Peripheral arteriolar occlusion

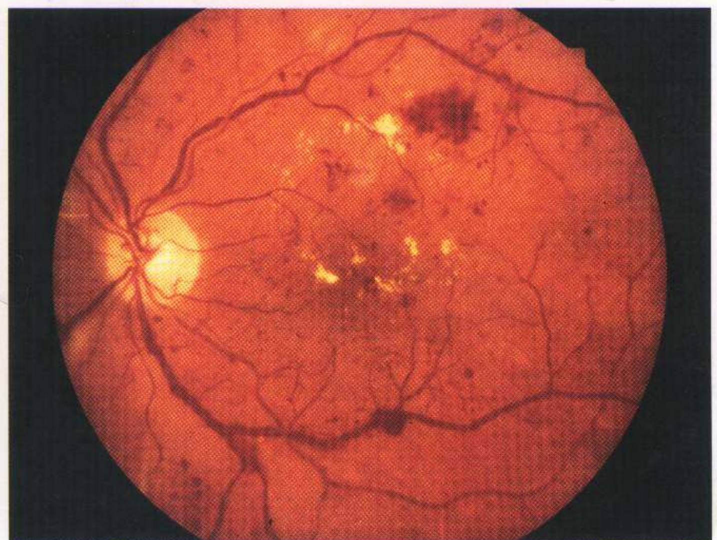


Fig. 14.22
Preproliferative diabetic retinopathy. Venous dilatation, looping and intraretinal microvascular abnormalities along the inferotemporal arcade, blot haemorrhages inside the superotemporal arcade and hard exudates at the macula

3. **Venous changes** consist of dilatation (*see* Fig. 14.16a and b), looping (Fig. 14.19), beading (Fig. 14.20) and 'sausage-like' segmentation.
4. **Arterial changes** consisting of narrowing, silver-wiring and obliteration resembling a branch retinal artery occlusion (Fig. 14.21).
5. **Dark blot haemorrhages** (Fig. 14.22) represent haemorrhagic retinal infarcts and are located within the middle retinal layers.

Management

PPDR should be watched closely because of the risk of PDR. Treatment by photocoagulation is usually not appropriate unless regular follow-up is not possible, or vision in the fellow eye has been already lost due to proliferative disease.

Diabetic maculopathy

Involvement of the fovea by oedema and hard exudates or ischaemia (diabetic maculopathy) is the most common cause of visual impairment in diabetic patients, particularly those with type 2 diabetes.

Classification

1. **Focal exudative**
   a. Signs. Well-circumscribed retinal thickening associated with complete or incomplete rings of perifoveal hard exudates (Fig. 14.23b).
   b. FA shows late, focal hyperfluorescence due to leakage and good macular perfusion (Fig. 14.23c).
2. **Diffuse exudative**
   a. Signs. Diffuse retinal thickening, which may be associated with cystoid changes. Obliteration of landmarks

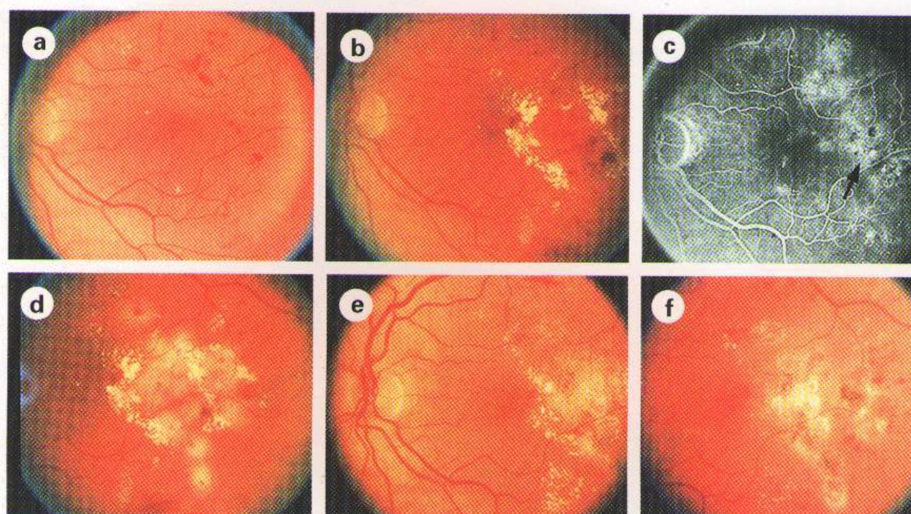


Fig. 14.23
Focal diabetic maculopathy. (**a**) Initial appearance showing only haemorrhages; (**b**) 2 years later showing a ring of hard exudates; (**c**) FA shows corresponding focal leakage; (**d**) appearance immediately following focal laser photocoagulation; (**e**) resolving hard exudates; (**f**) complete resolution of hard exudates and residual laser scars several months later (Courtesy of Wilmer Institute)

by severe oedema may render localization of the fovea impossible (Fig. 14.24a).

b. FA shows widespread spotty hyperfluorescence of microaneurysms (Fig. 14.24b) and late diffuse hyperfluorescence due to leakage, which is frequently more dramatic than on clinical examination, with a flower-petal pattern if CMO is present (Fig. 14.24c).

3. Ischaemic

a. Signs. Reduced visual acuity in association with a relatively normal appearance of the fovea (Fig. 14.25a). Associated PPDR is frequent. Dark blot haemorrhages may be seen.

b. FA shows capillary non-perfusion at the fovea (Fig. 14.25b), the severity of which does not always relate to the level of visual acuity. Other areas of capillary non-perfusion are also frequently present at the posterior pole and periphery.

4. Mixed is characterized by features of both ischaemia and exudation.

Clinically significant macular oedema

Definition

Clinically significant macular oedema (CSMO) has the following characteristics.

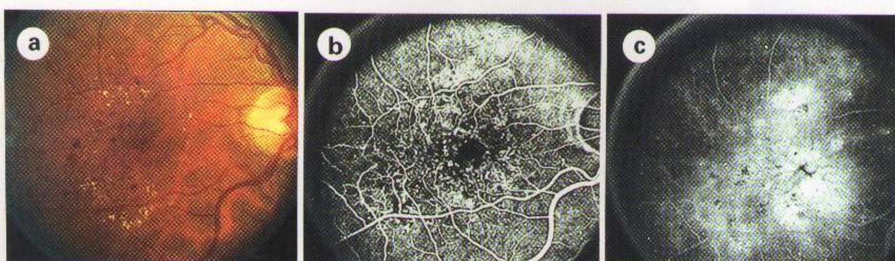


Fig. 14.24
Diffuse diabetic maculopathy. (**a**) A few hard exudates and dot haemorrhages; (**b**) early FA phase showing spotty hyperfluorescence of microaneurysms; (**c**) later phase FA showing extensive leakage and cystoid macular oedema (Courtesy of Wilmer Institute)



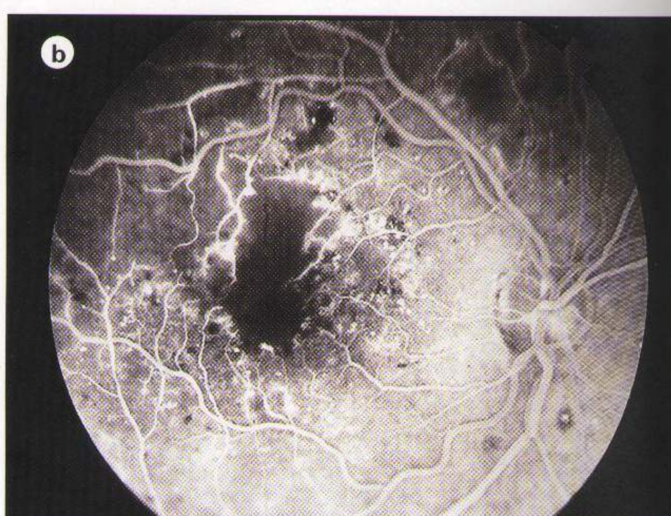


Fig. 14.25
Ischaemic diabetic maculopathy. (**a**) Dot and blot haemorrhages; (**b**) FA showing macular and peripheral non-perfusion

- Retinal oedema within 500 μm of the centre of the fovea (Fig. 14.26a).
- Hard exudates within 500 μm of the centre of the fovea, if associated with adjacent retinal thickening (which may be outside the 500 μm limit) (Fig. 14.26b).
- Retinal oedema one disc area (1500 μm) or larger, any part of which is within one disc diameter of the centre of the fovea (Fig. 14.26c).

NB: CSMO requires laser photocoagulation irrespective of the level of visual acuity because treatment reduces the risk of visual loss by 50%. Improvement of visual function is infrequent, rendering such treatment prophylactic. Pre-treatment FA is useful to delineate the area and extent of leakage and also to detect capillary non-perfusion at the fovea (ischaemic maculopathy) which carries a poor prognosis and is a contraindication to treatment.

Argon laser photocoagulation

1. Technique

a. Focal treatment involves applying laser burns to microaneurysms and microvascular lesions in the centre of rings of hard exudates located 500–3000 μm from the centre of the fovea (*see* Fig. 14.23d). The spot size is 50–100 μm with a duration of 0.10 seconds and sufficient power to obtain gentle whitening or darkening of the microaneurysm. Treatment of lesions up to 300 μm from the centre of the fovea may be considered if CSMO persists despite previous treatment and visual acuity is less than 6/12. In these cases a shorter exposure time of 0.05 seconds is recommended.

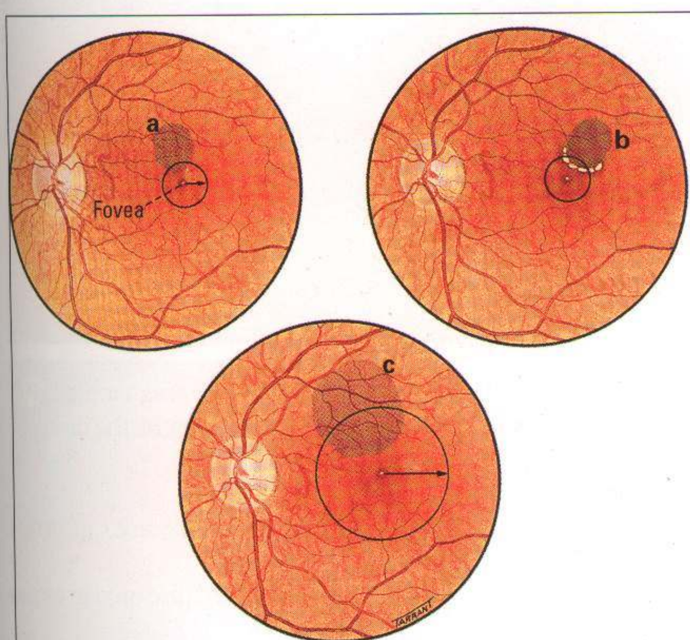


Fig. 14.26
Clinically significant macular oedema (see text)

b. Grid treatment is used for areas of diffuse retinal thickening located more than 500 μm from the centre of the fovea and 500 μm from the temporal margin of the optic disc. The spot size is 100–200 μm and exposure time 0.10 seconds. The burns should be of very light intensity and one burn-width apart.

2. Results. Approximately 70% of eyes achieve stable visual acuity, 15% show improvement and 15% subsequently deteriorate. Since it may take up to 4 months for the oedema to resolve (*see* Fig. 14.23f), re-treatment should not be considered prematurely.

3. Poor prognostic factors include:
- Hard exudates involving the fovea.
- Diffuse macular oedema.
- Cystoid macular oedema.
- Mixed exudative–ischaemic maculopathy.
- Severe retinopathy at presentation.

Vitrectomy

Pars plana vitrectomy may be indicated when macular oedema is associated with tangential traction from a thickened and taut posterior hyaloid membrane. In these cases laser therapy is of limited benefit but surgical release of tangential macular traction may be beneficial.

Proliferative diabetic retinopathy

PDR affects 5–10% of the diabetic population. Type 1 diabetics are at particular risk with an incidence of about 60% after 30 years. Protective factors include carotid occlusive disease, posterior vitreous separation, high myopia and optic atrophy.

Clinical features

1. Signs. Neovascularization is the hallmark of PDR. New vessels may proliferate on or within one disc diameter of the optic nerve head (NVD = new vessels at disc), or along the course of the major vessels (NVE = new vessels elsewhere), or both (Fig. 14.27a). It has been estimated that over one-quarter of the retina has to be non-perfused before PDR develops. The absence of the internal limiting membrane (ILM) at the optic nerve head may partially explain the predilection for neovascularization at this site. New vessels start as endothelial proliferations, arising most frequently from veins; they then pass through defects in the ILM to lie in the potential plane between the retina and posterior vitreous cortex, using the latter as a 'scaffold' for their growth (Fig. 14.27b).

2. FA, although not required to make the diagnosis (Fig. 14.28a), highlights the neovascularization during the early phases of the angiogram and shows hyperfluorescence during the later stages due to intense leakage of dye from neovascular tissue (Fig. 14.28b).

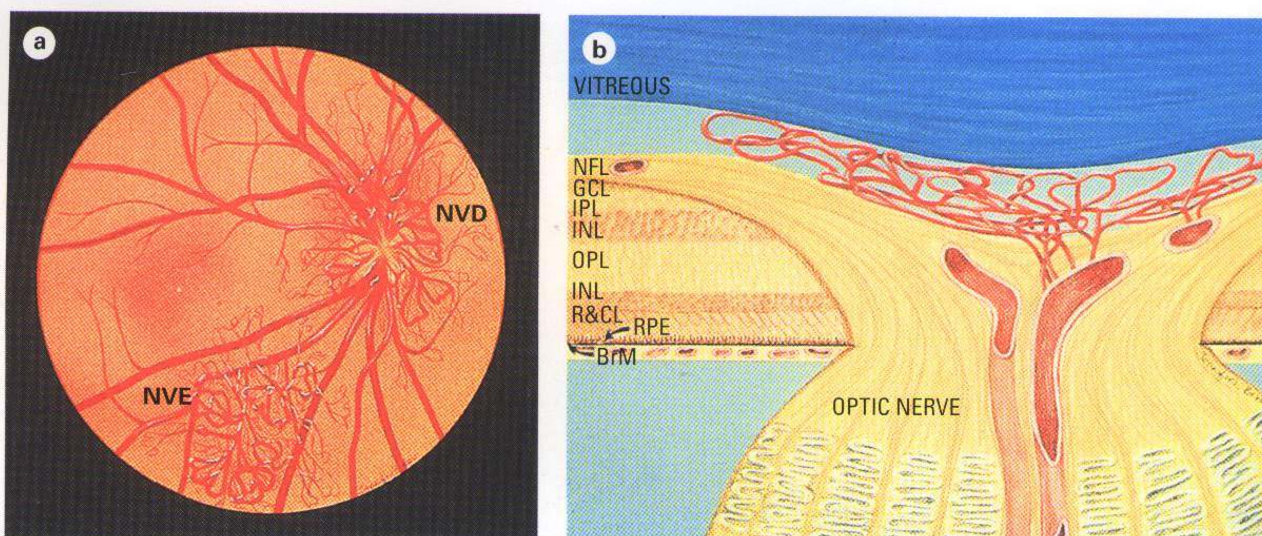
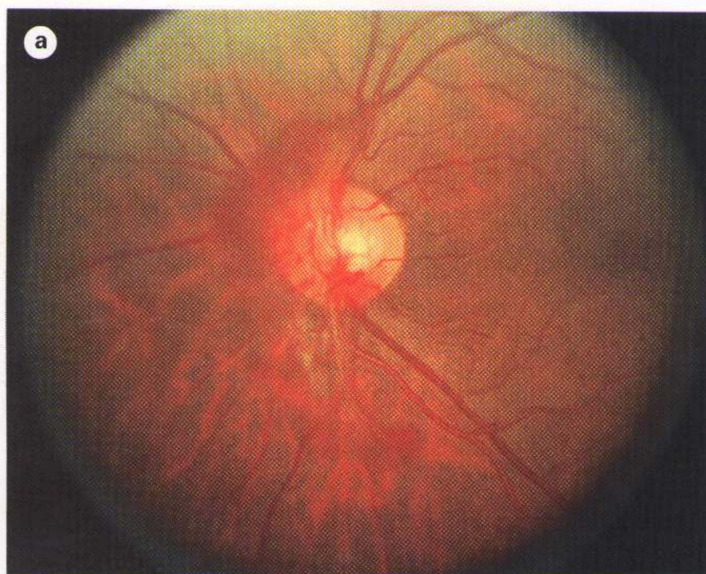


Fig. 14.27
Proliferative diabetic retinopathy. (**a**) Clinical features; (**b**) location of neovascularization (Courtesy of Wilmer Institute)



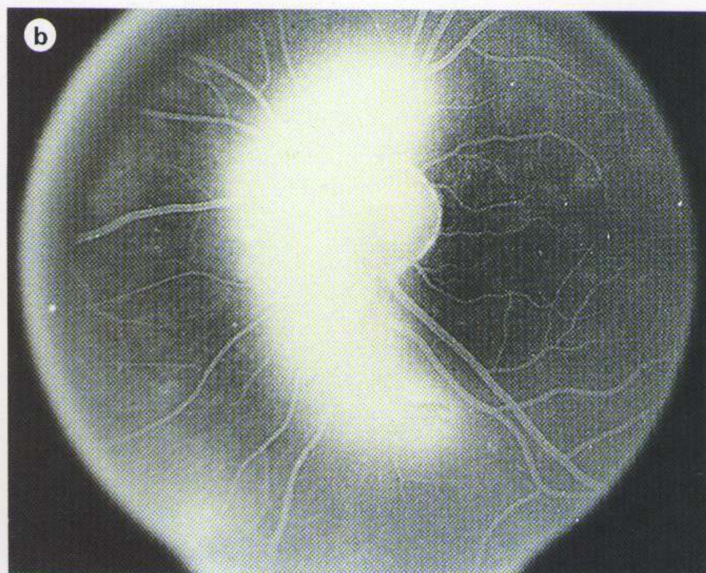


Fig. 14.28
(**a**) Disc new vessels; (**b**) late-phase FA shows extensive leakage (Courtesy of Wilmer Institute)

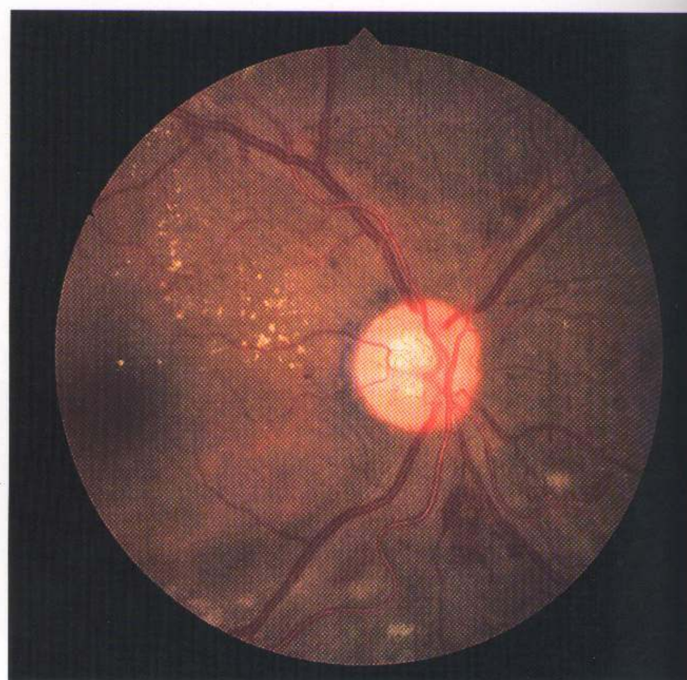


Fig. 14.29
Mild disc new vessels associated with severe preproliferative changes

Clinical assessment

1. Severity of PDR is determined by the area covered with new vessels in comparison with the area of the disc. The severity of PDR is described as follows:

a. NVD

- Mild when less than one-third disc area in extent (Fig. 14.29).
- Severe when more than one-third disc area in extent (Fig. 14.30).

b. NVE

- Mild if less than half disc area in extent (Fig. 14.31a).
- Severe if half disc area or more in extent (Fig. 14.32).

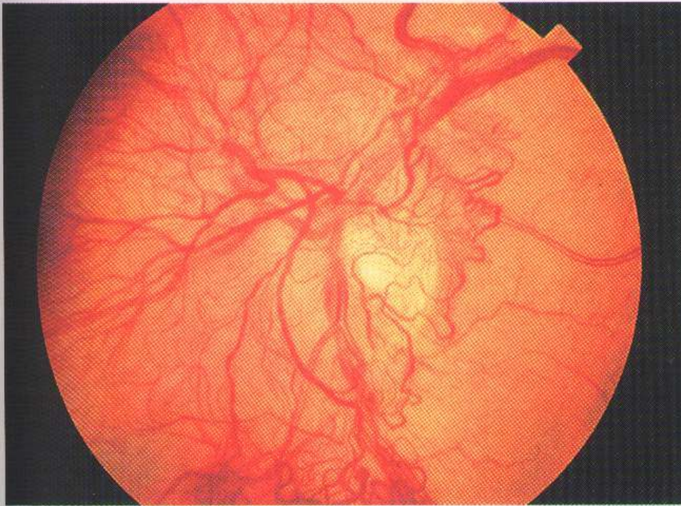


Fig. 14.30
Very severe disc new vessels

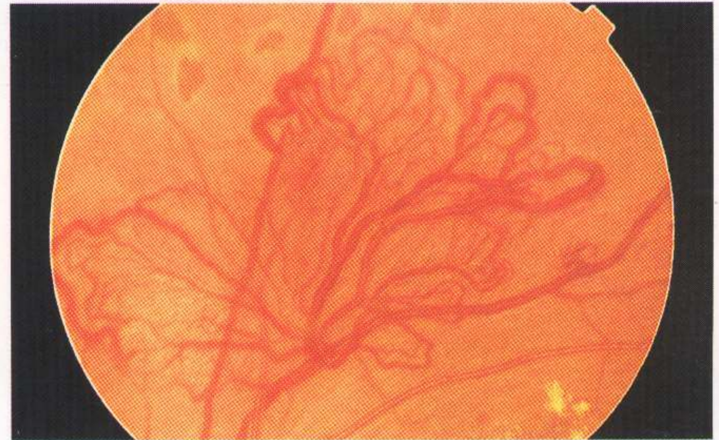


Fig. 14.32
Severe new vessels elsewhere

2. **Elevated** new vessels (Fig. 14.33 and *see* Fig. 14.31b–d) are less responsive to laser therapy than flat new vessels.
3. **Fibrosis** associated with neovascularization is important, since significant fibrous proliferation (Fig. 14.34), although less likely to bleed, carries an increased risk of tractional retinal detachment.
4. **Haemorrhage** which may be preretinal (subhyaloid) (Fig. 14.35) and/or intragel vitreous is an important risk factor for visual loss.
5. **High risk characteristics**. The following signify a high risk of severe visual loss within 2 years, if left untreated:
   - Mild NVD with haemorrhage (*see* Fig. 14.35a) carries a 26% risk of visual loss, which is reduced to 4% with treatment (*see* Fig. 14.35b).
   - Severe NVD without haemorrhage (*see* Fig. 14.30) carries a 26% risk of visual loss, which is reduced to 9% with treatment.
   - Severe NVD with haemorrhage (Fig. 14.36b) carries a 37% risk of visual loss, which is reduced to 20% with treatment (Fig. 14.36c and d).
   - Severe NVE with haemorrhage carries a 30% risk of visual loss, which is reduced to 7% with treatment.

NB: Unless the above criteria apply, it is recommended that photocoagulation be withheld and the patient be followed up at 3-monthly intervals. In practice, however, most ophthalmologists perform laser photocoagulation at the first sign of neovascularization.

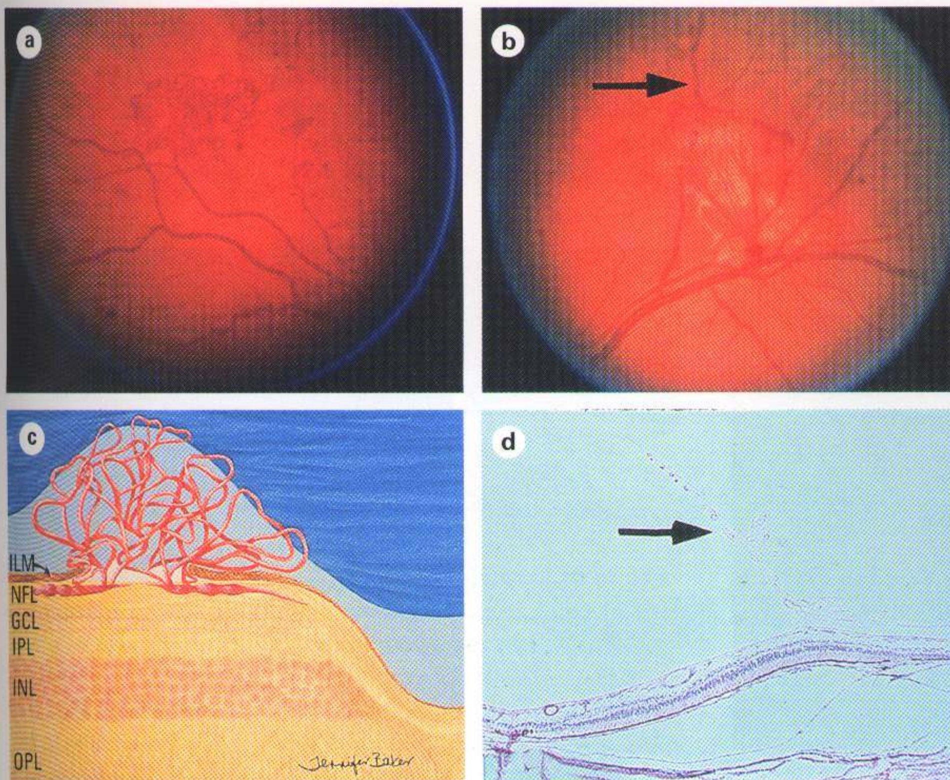


Fig. 14.31
Proliferative diabetic retinopathy; (**a**) flat new vessels elsewhere without fibrosis; (**b**) elevated new vessels elsewhere with fibrosis; (**c**) elevated new vessels elsewhere with partial vitreous separation; (**d**) histological section showing elevated new vessels elsewhere (Courtesy of Wilmer Institute)

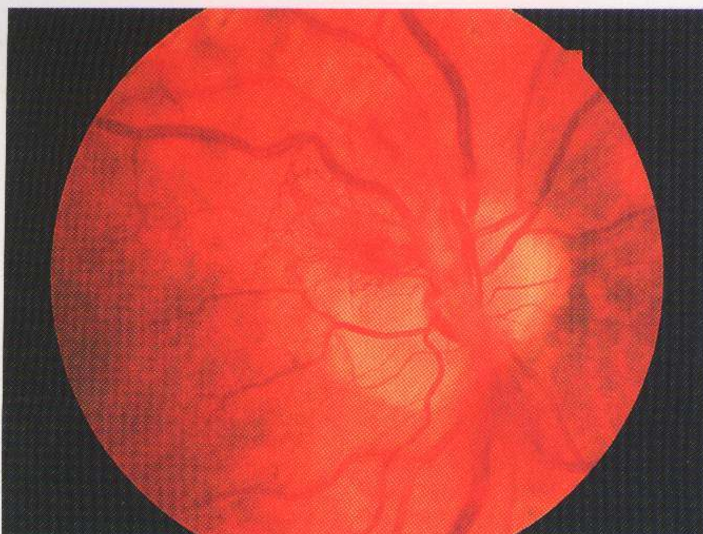
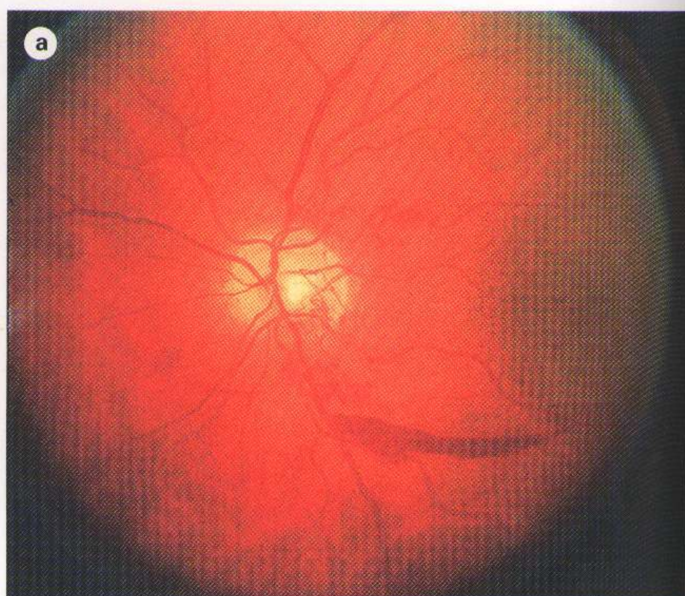


Fig. 14.33
Severe elevated disc new vessels



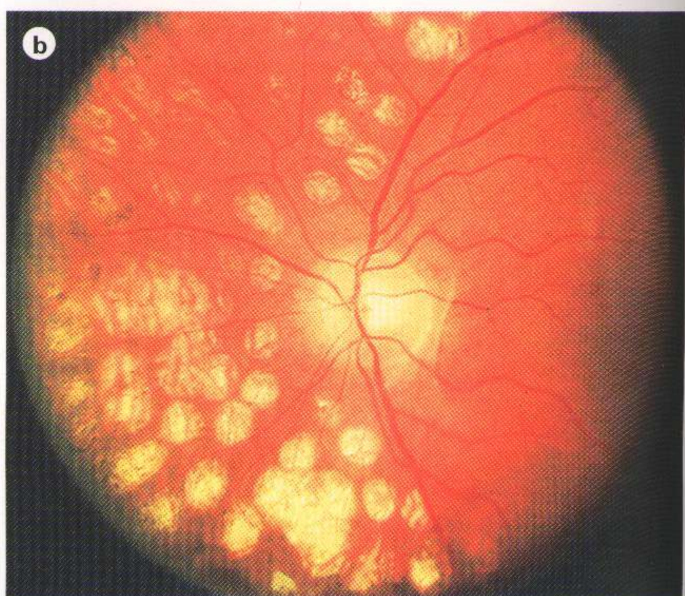


Fig. 14.35
Proliferative diabetic retinopathy (**a**); mild disc new vessels with preretinal haemorrhage; (**b**) involution following laser panretinal photocoagulation (Courtesy of Wilmer Institute)

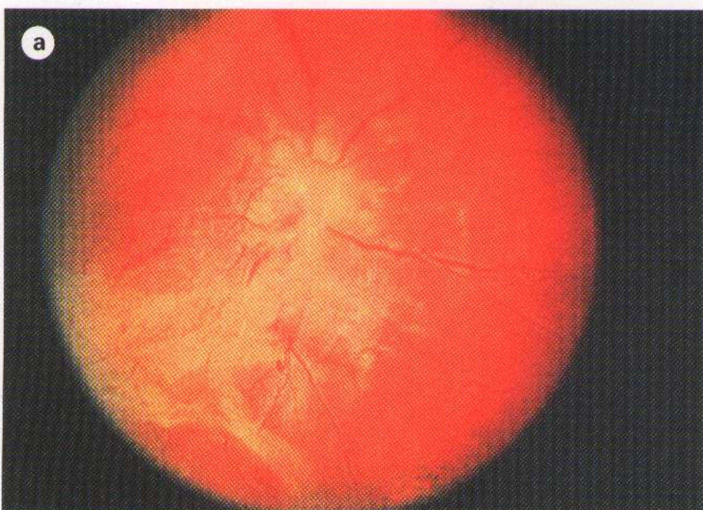
Panretinal laser photocoagulation (PRP)

Laser therapy is aimed at inducing involution of new vessels and preventing visual loss from vitreous haemorrhage and tractional retinal detachment. The extent of treatment is dependent on the severity of PDR. Laser burns are placed further apart with less intensity (Fig. 14.37a and b) for mild disease and closer together and with greater intensity (Fig. 14.37c and d) for severe or recurrent disease.

> ***NB:*** In the beginner's hands, a panfundoscopic lens is perhaps safer than the Goldmann three-mirror lens, since it is relatively easy to inadvertently photocoagulate the posterior pole through the latter, with disastrous consequences.

1. Laser settings

a. ***Spot size*** depends on the contact lens used. With the Goldmann lens, spot size is set at 500 μm, but with a panfundoscopic lens it is set at 300–200 μm because of induced magnification.



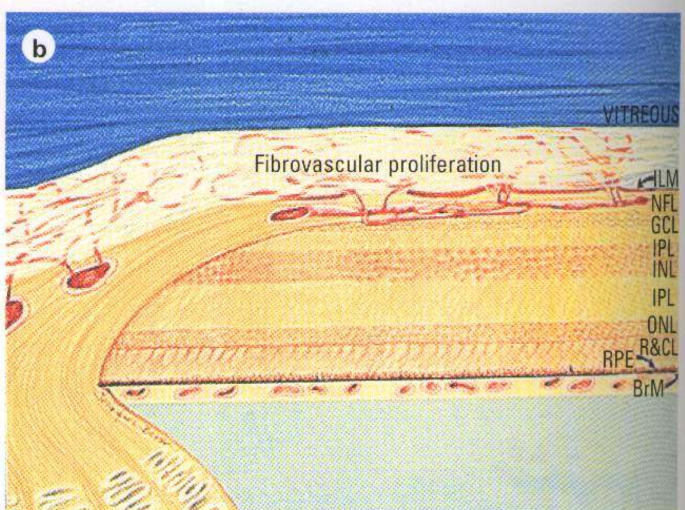


Fig. 14.34
Proliferative diabetic retinopathy (**a**); fibrovascular proliferation; (**b**) location between the internal limiting membrane and vitreous gel (Courtesy of Wilmer Institute)

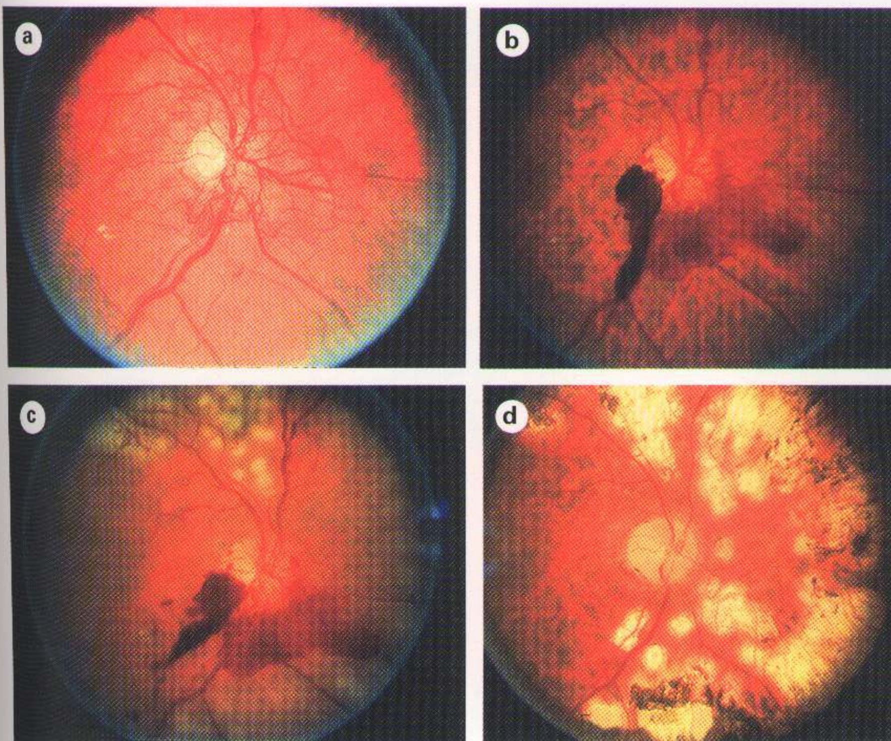


Fig. 14.36
Proliferative diabetic retinopathy; (**a**) severe disc new vessels; (**b**) preretinal and vitreous haemorrhage a few days later;
(**c**) appearance immediately following laser panretinal photocoagulation; (**d**) appearance 3 months later showing involution of new vessels and heavy laser scars (Courtesy of Wilmer Institute)

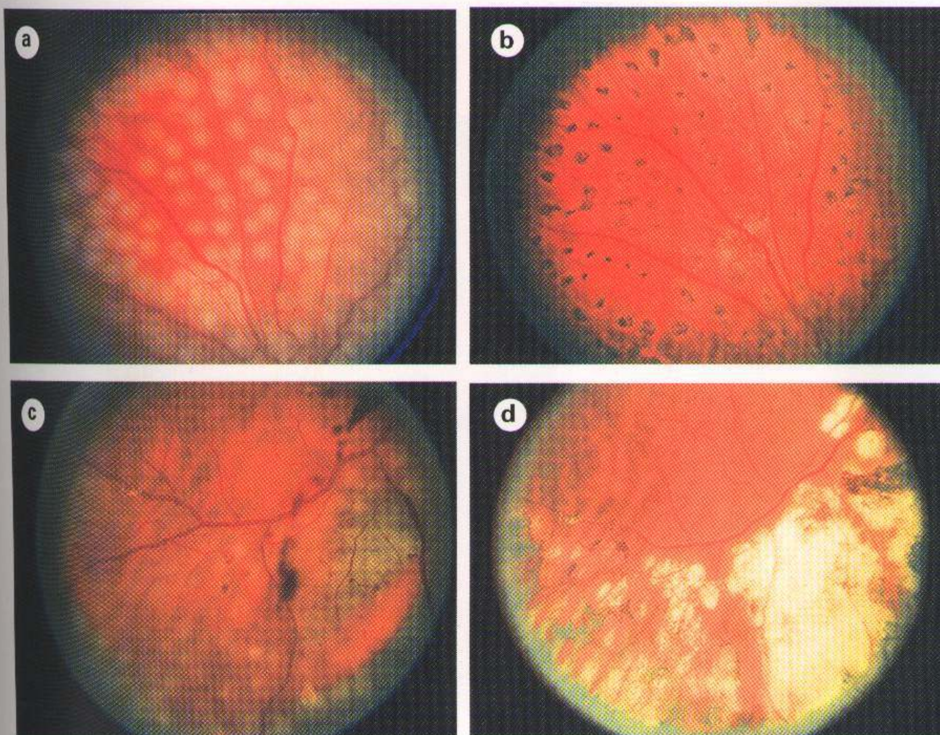


Fig. 14.37
Laser panretinal photocoagulation.
(**a** and **b**) Standard; (**c** and **d**) intensive
(Courtesy of Wilmer Institute)

b. *Duration* of the burn is 0.05–0.10 seconds at a power level that produces a gentle burn.

2. **Initial treatment** involves 2000–3000 burns in a scatter pattern, extending from the posterior fundus to cover the peripheral retina in one or more sessions. PRP completed in a single session carries a slightly higher risk of complications. The amount of treatment during any one session is governed by the patient's pain threshold and ability to maintain concentration. Topical corneal anaesthesia is adequate in most patients, although peribulbar or

3. **Sequence** is as follows:
   - *Step 1*. Close to the disc (Fig. 14.38a); below the inferior temporal arcades (Fig. 14.38b).
   - *Step 2*. Protective barrier around the macula (Fig. 14.39a) to prevent inadvertent treatment of the fovea; above the superotemporal arcade (Fig. 14.39b).
   - *Step 3*. Nasal to the disc (Fig. 14.40a); completion of posterior pole treatment (Fig. 14.40b).
   - *Step 4*. Peripheral treatment (Fig. 14.41a) until completion (Fig. 14.41b).

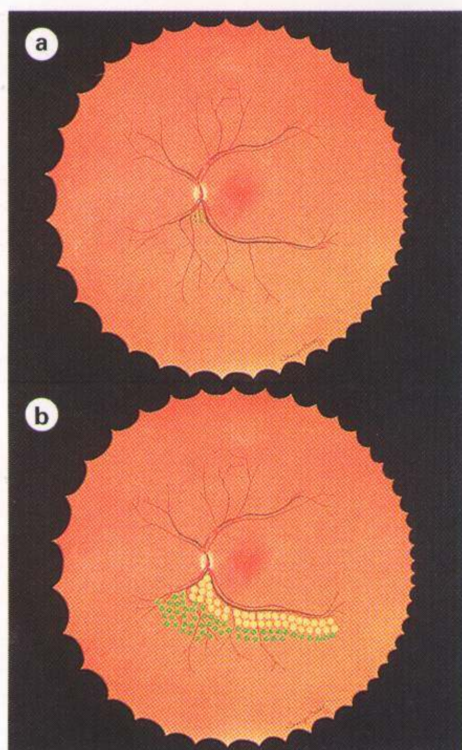


Fig. 14.38
Panretinal photocoagulation: step 1 (*see text*) (Courtesy of Wilmer Institute)

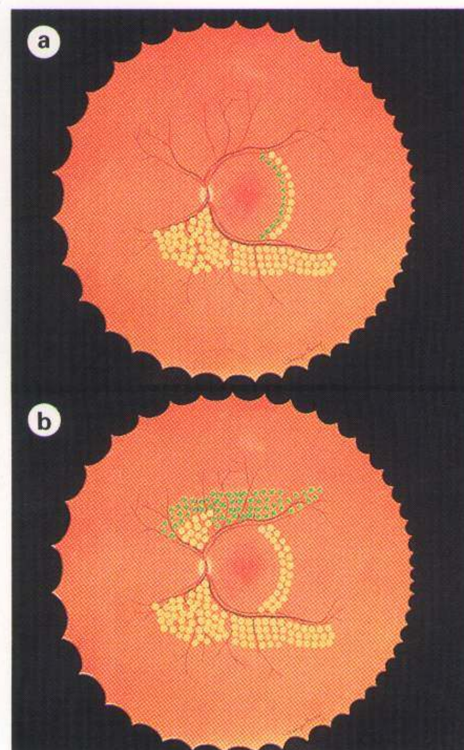


Fig. 14.39
Panretinal photocoagulation: step 2 (*see text*) (Courtesy of Wilmer Institute)

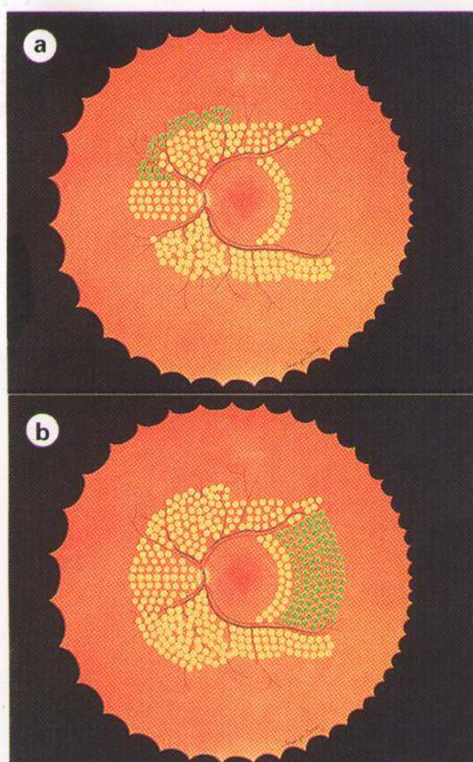


Fig. 14.40
Panretinal photocoagulation: step 3 (*see text*) (Courtesy of Wilmer Institute)

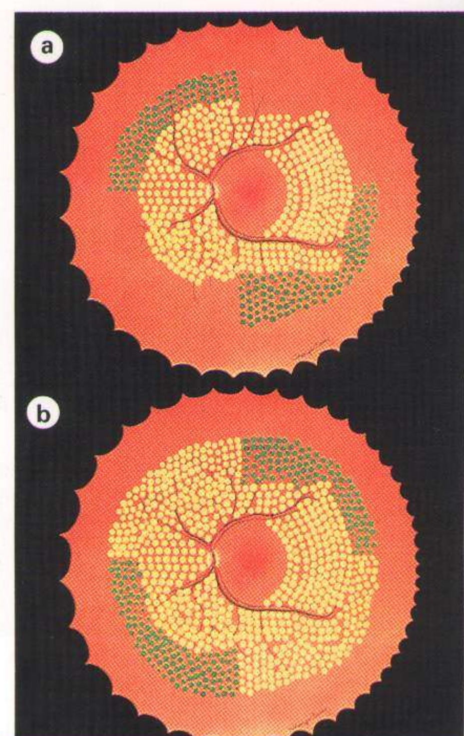
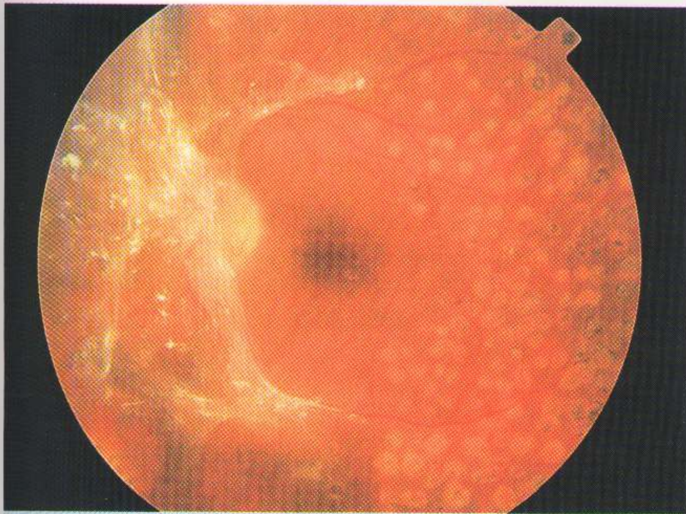


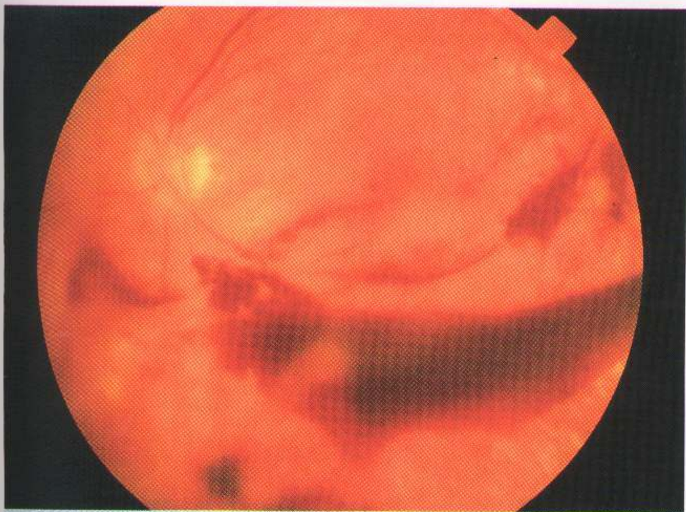
Fig. 14.41
Panretinal photocoagulation: step 4 (*see text*) (Courtesy of Wilmer Institute)

> ***NB:*** In very severe PDR it is advisable to treat the inferior fundus first, since any vitreous haemorrhage will gravitate inferiorly and obscure this area, precluding further treatment.

Subsequent management

1. **Follow-up** is after 4–6 weeks. In eyes with severe NVD, several treatment sessions totalling 5000 or even more burns may be required, although complete elimination of


Fig. 14.42
Residual glial tissue following panretinal photocoagulation (Courtesy of S. Milewski)


Fig. 14.43
Preretinal and intragel haemorrhage

NVD may be difficult and early vitreous surgery may be necessary. The most important cause of persistent neovascularization is inadequate treatment.

2. **Signs of involution** are regression of neovascularization leaving only 'ghost' vessels or fibrous tissue (*see* Fig. 14.35b), decrease in venous dilatation, absorption of retinal haemorrhages and disc pallor (*see* Fig. 14.36d). In most eyes, once the retinopathy is quiescent, stable vision is maintained. In a few eyes, recurrences of PDR occur despite an initial satisfactory response. It is therefore necessary to re-examine the patient at intervals of approximately 6–12 months.

> ***NB:*** PRP influences only the vascular component of the fibrovascular process. Eyes in which new vessels have regressed leaving only fibrous tissue (Fig. 14.42) should not be re-treated.

3. **Treatment of recurrence**
   a. *Further laser photocoagulation*, filling in any gaps between previous laser scars.
   b. *Cryotherapy* to the anterior retina is particularly useful when further photocoagulation is impossible as a result of inadequate visualization of the fundus caused by opaque media. It also offers a means of treating areas of the retina spared by PRP.

> ***NB:*** It should be explained to patients that PRP may result in visual field defects of sufficient severity to legally preclude driving a motor vehicle.

Advanced diabetic eye disease

Serious vision-threatening complications of diabetic retinopathy (advanced diabetic eye disease) occur in patients who have not had laser therapy or in whom laser photocoagulation has been unsuccessful or inadequate. One or more of the following complications may occur.

Haemorrhage

This may occur into the vitreous gel, the retrohyaloid space (preretinal haemorrhage) or both (Fig. 14.43). A preretinal haemorrhage has a crescentic shape which demarcates the level of posterior vitreous detachment. Occasionally, a preretinal haemorrhage may penetrate the vitreous gel. Intragel haemorrhages usually take longer to clear than preretinal haemorrhages. In some eyes, altered blood becomes compacted on the posterior vitreous face to form an 'ochre membrane'. Patients should be warned that bleeding may be precipitated by severe physical exertion or straining, hypoglycaemia and direct ocular trauma. However, not infrequently bleeding occurs while the patient is asleep.

Tractional retinal detachment

This is caused by progressive contraction of fibrovascular membranes over large areas of vitreoretinal adhesion. Posterior vitreous detachment in diabetic eyes is gradual and, due to the strong adhesions of cortical vitreous to areas of fibrovascular proliferation, is usually incomplete.

1. **Pathogenesis**. The following types of static vitreoretinal traction may result in retinal detachment:
   a. *Anteroposterior* traction due to contraction of fibrovascular membranes extending from the posterior retina, usually in association with the major vascular arcades, to the vitreous base anteriorly (Fig. 14.44).
   b. *Bridging* (trampoline) traction is the result of contraction of fibrovascular membranes stretching from one part of the posterior retina to another (Fig. 14.45). This tends to pull the two involved points together and may result in the formation of stress lines as well as displacement of the macula towards the disc or elsewhere, depending on the direction of the tractional force.
2. **Signs** (*see* Chapter 12).

Other complications

1. **Opaque membranes** may develop on the posterior surface of the detached hyaloid and stretch from the superior to the

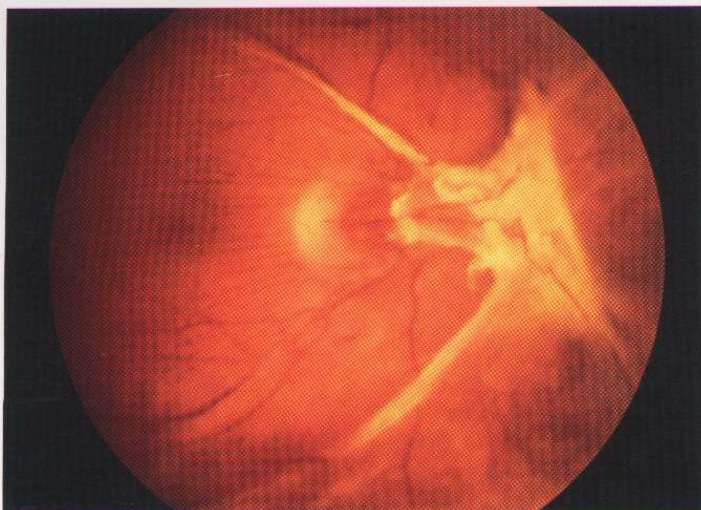


Fig. 14.44
Anteroposterior traction resulting in elevation of fibrovascular tissue

inferior temporal arcades (Fig. 14.46). Such membranes may obscure the macula and further impair visual acuity.

2. **Rubeosis iridis** (iris neovascularization) may occur in eyes with PDR, and if severe may lead to neovascular glaucoma (*see* Chapter 9). Rubeosis is particularly common in eyes with severe retinal ischaemia or persistent retinal detachment following unsuccessful pars plana vitrectomy.

Pars plana vitrectomy

This is the main method of treating severe complications of PDR.

1. **Indications**
   a. ***Severe persistent vitreous haemorrhage*** is the most common indication. In these cases the density of the haemorrhage precludes adequate PRP. In the absence of

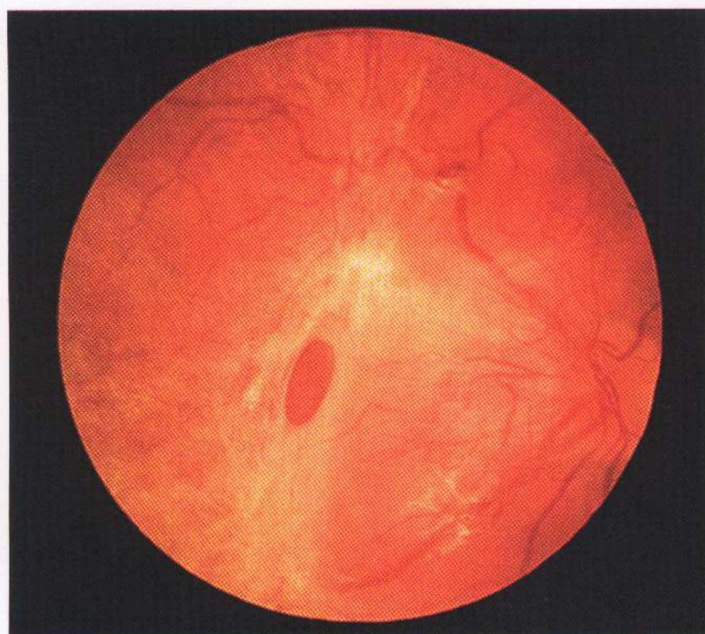


Fig. 14.45
Bridging traction resulting in contraction of fibrovascular tissue between the temporal arcades

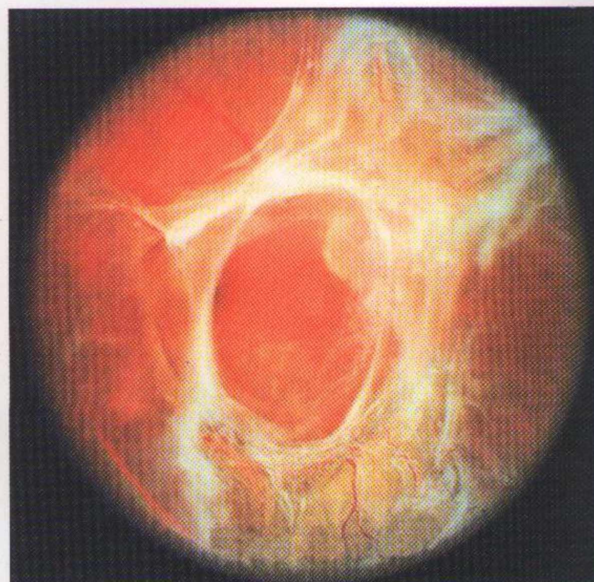


Fig. 14.46
Extensive avascular glial tissue and a localized inferior tractional retinal detachment in inactive proliferative diabetic retinopathy (Courtesy of Wilmer Institute)

rubeosis iridis, vitrectomy within 3 months of the initial vitreous haemorrhage should be considered in type 1 diabetics and at about 6 months in type 2 diabetics.

   b. ***Tractional RD*** threatening or involving the macula must be treated without delay. However, extra-macular tractional detachments may be observed, since they often remain stationary for prolonged periods of time.
   c. ***Combined tractional and rhegmatogenous RD*** should be treated urgently, even if the macula is not involved, because subretinal fluid is likely to spread quickly to involve the macula.
   d. ***Premacular subhyaloid haemorrhage***, if dense (Fig. 14.47) and persistent, should be considered for vitrectomy because, if untreated, the internal limiting membrane or posterior hyaloid face may serve as a scaffold for subsequent fibrovascular proliferation and

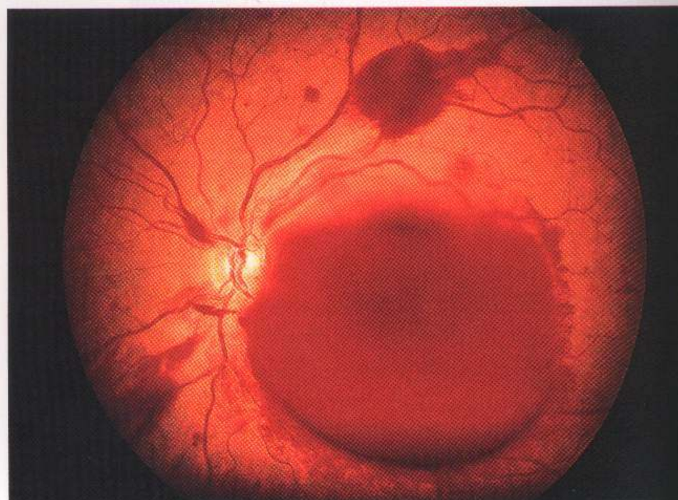


Fig. 14.47
Preretinal haemorrhage obscuring the posterior pole

subsequent tractional macular detachment or macular pucker caused by contraction of epiretinal membranes.

e. Macular oedema may occasionally benefit from pars plana vitrectomy as previously mentioned.

2. Aims

a. Removal of vitreous gel, thus eliminating the scaffold along which further fibrovascular tissue can proliferate. If this goal is achieved, involution of existing neovascular tissue also frequently occurs.

b. Removal of vitreous haemorrhage.

c. Repair of RD by excising tractional membranes (Fig. 14.48a) and removing fibrovascular tissue from the retinal surface. Any retinal breaks should also be sealed.

d. Prevention of further neovascularization by laser endophotocoagulation (Fig. 14.48b).

3. Complications

a. Progressive rubeosis iridis is the most common anterior segment complication resulting in failure. It has an increased incidence in aphakic eyes and in those with residual areas of detached retina. In eyes with total retinal detachments the incidence of rubeosis is virtually 100%.

b. Cataract may be the result of progression of pre-existing lens opacities or surgical trauma.

c. Glaucoma may be secondary to rubeosis or may be of the ghost cell or red cell type (*see* Chapter 9).

d. Recurrent vitreous haemorrhage may be caused by fresh fibrovascular proliferation.

e. Retinal detachment may be caused by operative complications, such as traction on the vitreous base or the inadvertent creation of fresh breaks with the cutter or other instruments. It may also occur later as a result of fresh fibrovascular proliferation.

4. Visual results depend on the specific indications for surgery and the complexity of pre-existing vitreoretinal abnormalities. In general, about 70% of cases achieve visual improvement, about 10% are made worse and the remainder have no change in vision. It appears that the first few postoperative months are vital. If an eye is doing well after 6 months, then the long-term outlook is favourable because the incidence of subsequent vision-threatening complications is low. Factors associated with a favourable prognosis are:

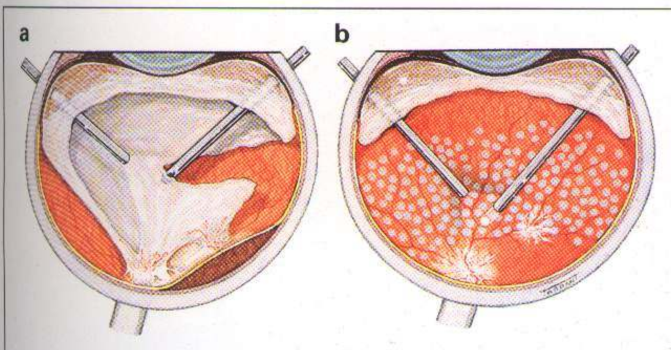


Fig. 14.48
Principles of vitreous surgery for advanced diabetic eye disease. (a) Retinal reattachment by excision of tractional forces; (b) endophotocoagulation

- Good preoperative visual function.
- Age of 40 years or less.
- Absence of preoperative rubeosis iridis and glaucoma.
- PRP of at least one-quarter of the fundus.

Screening for diabetic retinopathy

All diabetics aged over 12 years and/or entering puberty should be screened, and those with risk factors for visual loss referred to an ophthalmologist. Screening involves measurement of visual acuity for distance and near, and fundus examination following pupillary dilatation with tropicamide 1%.

1. Annual review but referral not appropriate
- Normal fundus.
- Mild BDR with small haemorrhages and/or small hard exudates more than one disc diameter from the fovea.

2. Routine referral to ophthalmologist
- BDR with large circinate exudates within the major temporal arcades but not threatening the fovea.
- BDR without maculopathy but with reduced visual acuity to determine the cause of visual impairment.

3. Early referral to ophthalmologist
- BDR with hard exudates and/or haemorrhages within one disc diameter from the fovea.
- Maculopathy.
- PPDR.

4. Urgent referral to ophthalmologist
- PDR.
- Preretinal or vitreous haemorrhage.
- Rubeosis iridis.
- Retinal detachment.

Retinal vein occlusion

Introduction

Classification

1. Branch retinal vein occlusion (BRVO).

2. Central retinal vein occlusion (CRVO).
- Non-ischaemic.
- Ischaemic.
- Papillophlebitis.

3. Hemiretinal vein occlusion.

Pathogenesis

Arteriolosclerosis is an important contributing factor for BRVO. Because a retinal arteriole and its corresponding vein share a common adventitial sheath, thickening of the arteriole appears to compress the vein if the arteriole is anterior to the vein. This causes secondary changes, including venous endothelial cell loss, thrombus formation

and eventually occlusion. Similarly, the central retinal vein and artery share a common adventitial sheath posterior to the lamina cribrosa so that atherosclerotic changes of the artery may compress the vein and precipitate CRVO. It therefore appears that both arterial and venous disease contribute to retinal vein occlusion. Venous occlusion causes elevation of venous and capillary pressure with stagnation of blood flow. Stagnation results in hypoxia of the retina drained by the obstructed vein, which in turn results in damage to the capillary endothelial cells and extravasation of blood constituents. The tissue pressure is increased, causing further stagnation of the circulation and hypoxia, so that a vicious cycle is established.

Underlying associations

In order of importance the following conditions are associated with an increased risk of retinal vein occlusion:

1. **Advancing age** is the most important factor; over 50% of cases occur in patients over the age of 65 years.
2. **Systemic** conditions include hypertension, hyperlipidaemia, diabetes, smoking and obesity.
3. **Raised intraocular pressure** (e.g. primary open-angle glaucoma, ocular hypertension) increases the risk of CRVO.
4. **Inflammatory** diseases such as sarcoidosis and Behçet disease may be associated with occlusive retinal periphlebitis.
5. **Hyperviscosity** associated with polycythaemia or abnormal plasma proteins (e.g. myeloma, Waldenström macroglobulinaemia).
6. **Acquired thrombophilic** disorders include hyperhomocysteinaemia and antiphospholipid antibody syndrome. Elevated plasma homocysteine is also a risk factor for myocardial infarction, stroke and carotid disease as well as CRVO, particularly the ischaemic type. Hyperhomocysteinaemia is readily reversible in most cases with folic acid.
7. **Inherited thrombophilic** disorders may be associated with venous occlusion in young adults. These include increased levels of clotting factors VII and XI, deficiencies of anticoagulants such as antithrombin III, protein C and S, and resistance to activated protein C (factor V Leiden).

> *NB:* Factors that appear to decrease the risk of venous occlusion include increased physical activity and moderate alcohol consumption.

Branch retinal vein occlusion

Classification

1. **Major branch vein occlusion** may be subdivided as follows:
   - Occlusion of a first-order temporal branch at the optic disc (Fig. 14.49a and *see* Fig. 14.52a)).
- Occlusion of a first-order temporal branch away from the disc but involving the branches to the macula (Figs 14.49b and 14.50).

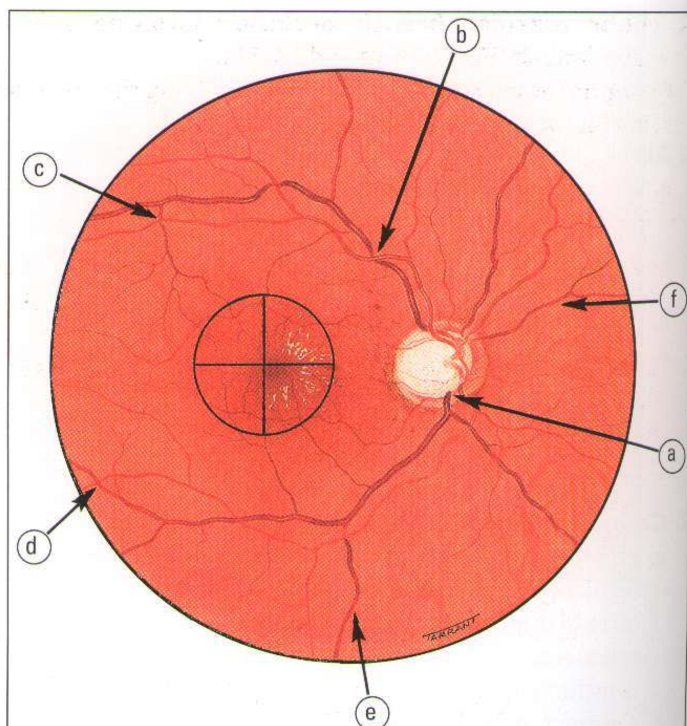


Fig. 14.49
Classification of retinal branch vein occlusion according to site of blockage (*see text*)

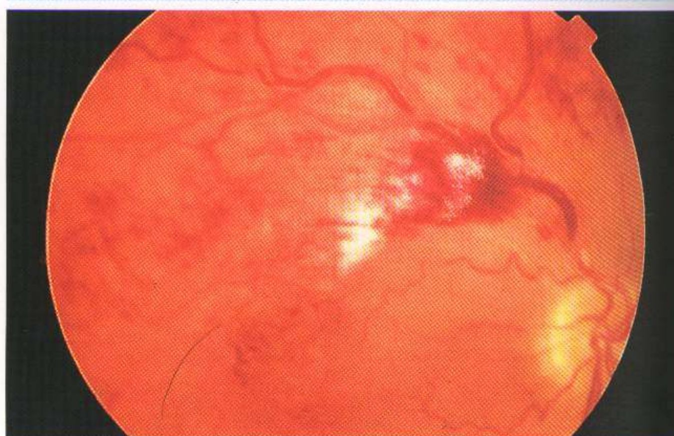


Fig. 14.50
Superotemporal branch retinal vein occlusion

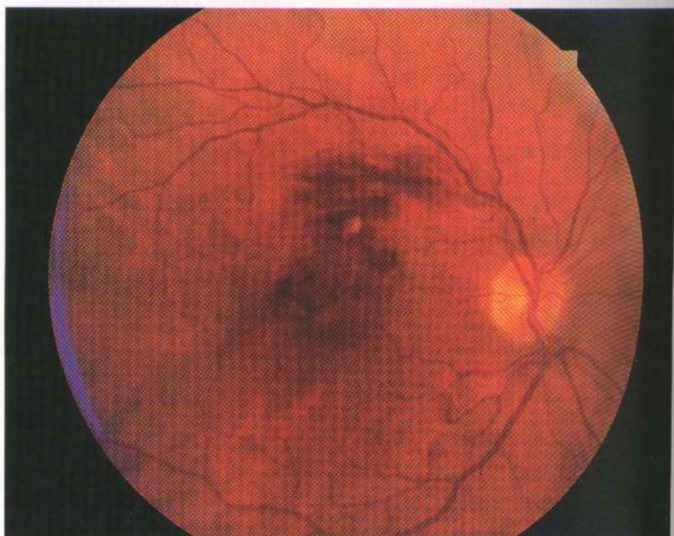


Fig. 14.51
Macular branch retinal vein occlusion

2. **Minor macular branch occlusion** involving only a macular branch (Figs 14.49c and 14.51).
3. **Peripheral branch occlusion** not involving the macular circulation (Fig. 14.49d–f).

Clinical features

1. **Presentation** depends on the amount of macular drainage compromised by the occlusion. Patients with macular involvement often present with sudden onset of blurred vision and metamorphopsia or a relative visual field defect. Patients with peripheral occlusions may be asymptomatic.
2. **Visual acuity** is variable and dependent on the extent of macular involvement.
3. **Fundus** (Fig. 14.52a)
   - Venous dilatation and tortuosity peripheral to the site of occlusion.
   - Flame-shaped and dot-blot haemorrhages, retinal oedema, and cotton wool spots affecting the sector of the retina drained by the obstructed vein.
4. **FA** during the early phases shows hypofluorescence due to blockage of background choroidal fluorescence by retinal haemorrhages (Fig. 14.52b and c). The late phase shows hyperfluorescence due to leakage (Fig. 14.52d).
5. **Course.** The acute features take 6–12 months to resolve and may be replaced by the following:
   - Venous sheathing and sclerosis peripheral to the site of obstruction with variable amount of residual haemorrhage (Fig. 14.53).
   - Collateral venous channels, characterized by slightly tortuous vessels, develop locally (Fig. 14.54), across the horizontal raphe between the inferior and superior vascular arcades, or at the optic disc (Fig. 14.55).
   - Microaneurysms and hard exudates (Fig. 14.56) may be associated with cholesterol crystal deposition.
   - The macula may show RPE changes or epiretinal gliosis.

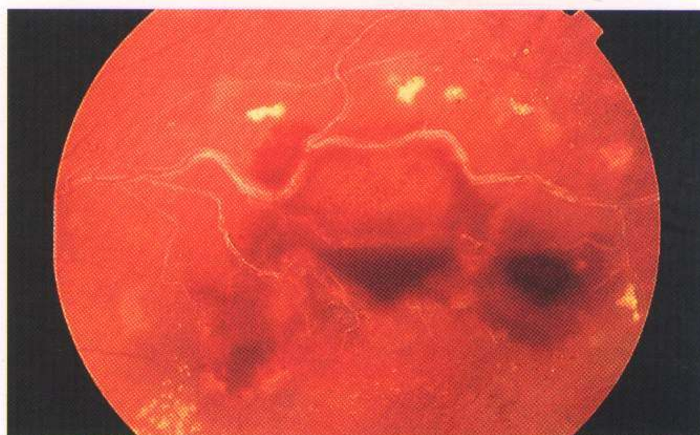


Fig. 14.53
Old superotemporal branch retinal vein occlusion showing venous sheathing, residual haemorrhages and a few hard exudates

Prognosis

This is reasonably good. Within 6 months about 50% of eyes develop efficient collaterals, with return of visual acuity to 6/12 or better. Eventual visual recovery depends on the amount of venous drainage involved by the occlusion (which is related to the site and size of the occluded vein) and the

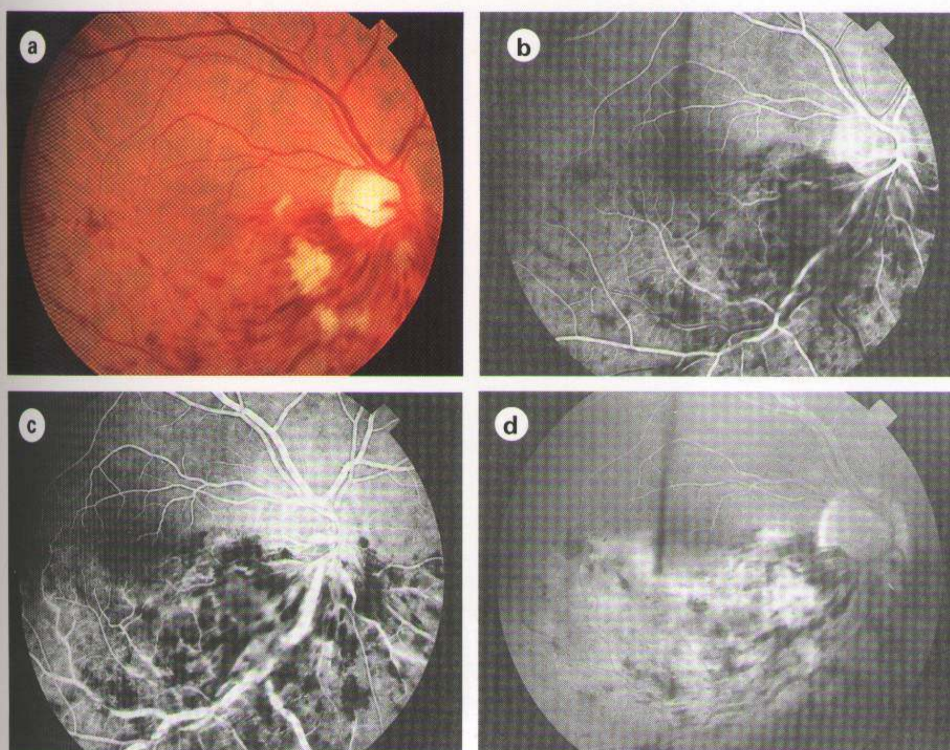


Fig. 14.52
(**a**) Major branch retinal vein occlusion; (**b** and **c**) venous phase FA showing hypofluorescence due to masking by blood and cotton wool spots; (**d**) late phase showing hyperfluorescence due to leakage (Courtesy of S. Milewski)

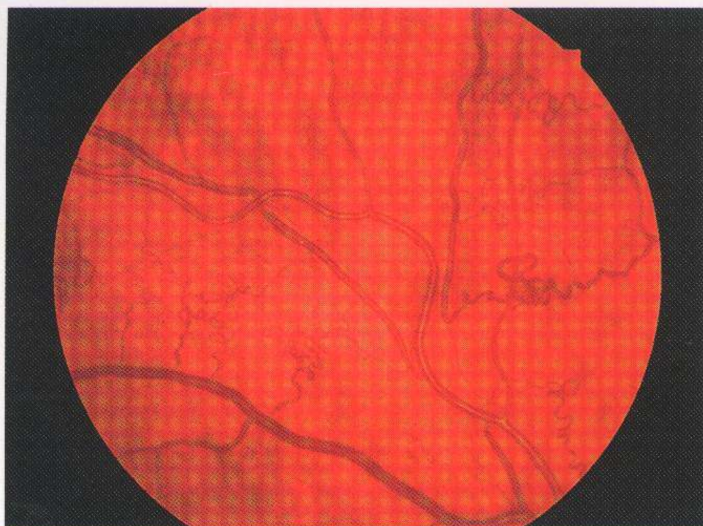


Fig. 14.54
Collaterals following branch retinal vein occlusion

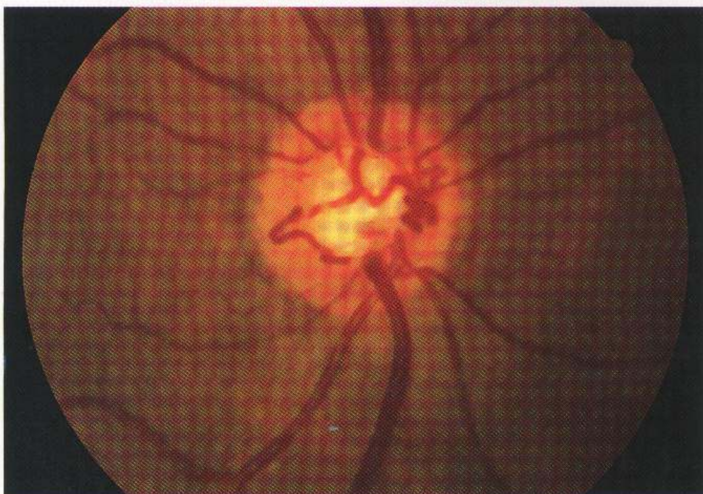


Fig. 14.55
Disc collaterals following non-ischaemic central retinal vein occlusion

severity of macular ischaemia. The two main vision-threatening complications are:

1. **Chronic macular oedema** is the most common cause of persistent poor visual acuity after BRVO. Some patients with visual acuity of 6/12 or worse may benefit from laser photocoagulation, provided the macula is oedematous rather than ischaemic.
2. **Neovascularization**. NVD develops in about 10% and NVE in 20–30% of eyes. The incidence of both increases with the severity and extent of involvement. NVE usually develops at the border of the triangular sector of ischaemic retina non-drained by the occluded vein. Neovascularization may develop at any time within the first 3 years but usually appears during the initial 6–12 months. It is a serious complication because it can lead to recurrent vitreous and preretinal haemorrhage, and occasionally tractional retinal detachment.

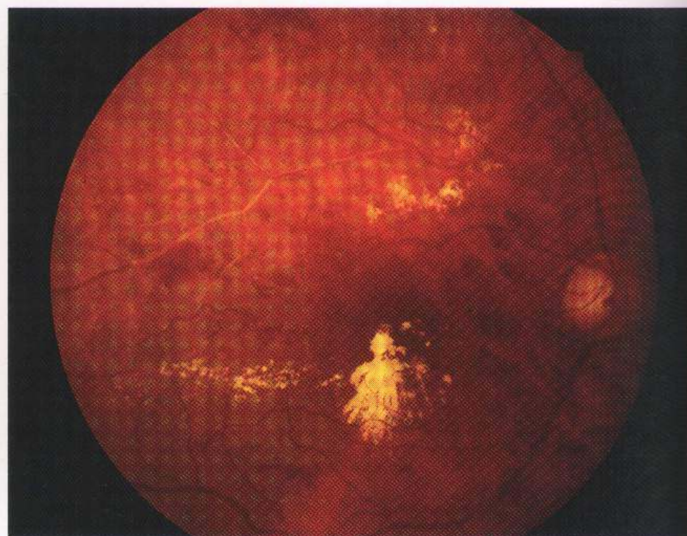


Fig. 14.56
Hard exudates at the macula following a superotemporal branch retinal vein occlusion

Follow-up

The patient should be reviewed at 6–12 weeks with FA, provided the retinal haemorrhages have cleared sufficiently. Further management depends on visual acuity and angiographic findings.

- FA shows good macular perfusion and visual acuity is improving—no treatment is required.
- FA shows macular oedema associated with good macular perfusion (Fig. 14.57) and visual acuity continues to be 6/12 or worse after 3 months—laser photocoagulation should be considered. However, prior to treatment, the FA should be studied carefully to identify the leaking areas. It

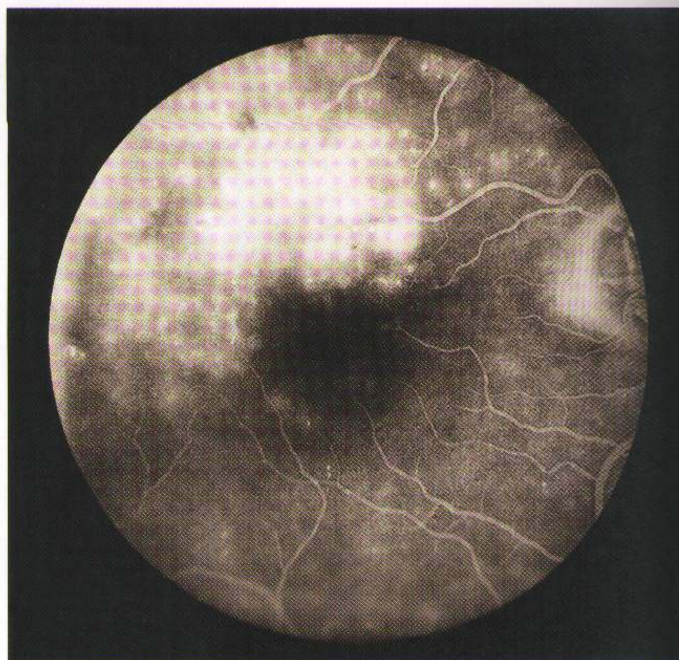


Fig. 14.57
FA showing extensive leakage but good macular perfusion following a superotemporal branch vein occlusion

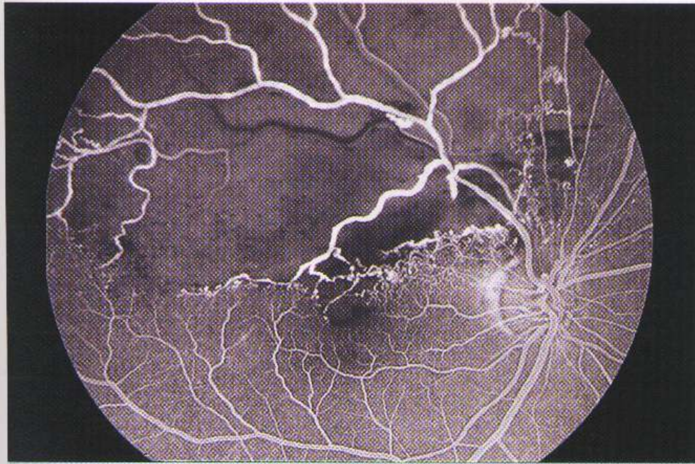


Fig. 14.58
FA showing extensive capillary closure following a superotemporal branch retinal vein occlusion

is also very important to identify collateral vessels, which do not leak fluorescein, because they must not be treated.

- FA shows macular non-perfusion (Fig. 14.58) and visual acuity is poor—laser treatment will not improve vision. However, if the FA shows five or more disc diameters of non-perfusion the patient should be reviewed at 4-monthly intervals for 12–24 months because of the risk of neovascularization.

Laser treatment

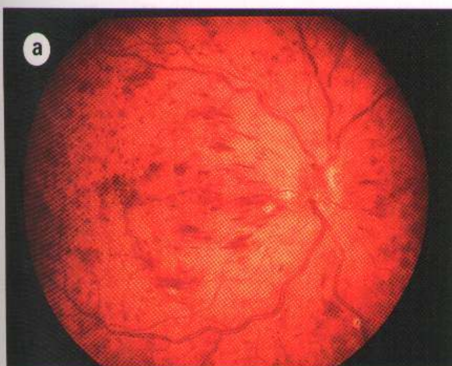
1. **Macular oedema** is treated by grid laser photocoagulation (50–100 μm burns spaced one burn apart) to produce a medium reaction to the area of leakage as identified on FA. The burns should extend no closer to the fovea than the edge of the FAZ and be no more peripheral than the major vascular arcades. Care should be taken to avoid treating over intraretinal haemorrhage. Follow-up should be after 2–3 months. If macular oedema persists re-treatment may be considered although the results may be disappointing.
2. **Neovascularization** is treated by scatter laser photocoagulation (200–500 μm burns one burn apart) to achieve a medium reaction covering the entire involved sector as defined by the colour photograph and FA. Follow-up should be after 4–6 weeks. If neovascularization persists re-treatment is frequently effective in inducing regression.

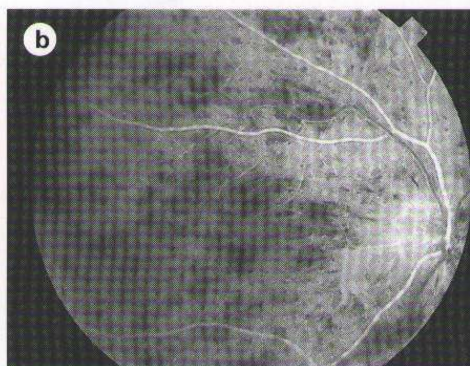
Non-ischaemic central retinal vein occlusion

Non-ischaemic CRVO is the most common type, accounting for about 75% of all cases.

Clinical features

1. **Presentation** is with sudden, unilateral blurred vision.
2. **Visual impairment** is moderate to severe.
3. **APD** (afferent pupillary defect) is absent or mild (in contrast to ischaemic CRVO).
4. **Fundus** (Fig. 14.59a)
   - Variable tortuosity and dilatation of all branches of the central retinal vein.
   - Retinal dot-blot and flame-shaped haemorrhages, throughout all four quadrants and most numerous in the periphery.
   - Occasional cotton wool spots.







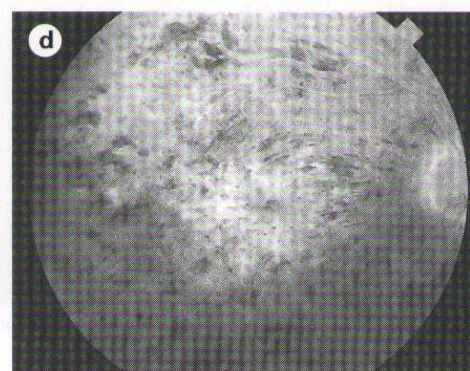


Fig. 14.59
(**a**) Non-ischaemic central retinal vein occlusion; (**b**) arteriovenous phase showing blockage of fluorescence by haemorrhages; (**c**) late venous phase showing early hyperfluorescence at the macula due to leakage; (**d**) late phase showing marked hyperfluorescence due to progressive leakage (Courtesy of S. Milewski)

- Mild to moderate optic disc oedema and macular oedema are common.

5. **FA** shows delayed venous return, good retinal capillary perfusion (Fig. 14.59b and c) and late leakage (Fig. 14.59d).
6. **Course**. Most acute signs resolve over 6–12 months. Residual findings include disc collaterals, epiretinal gliosis and pigmentary changes at the macula. Conversion to ischaemic CRVO occurs in 15% of cases within 4 months and 34% within 3 years.

Prognosis

In cases that do not subsequently become ischaemic, prognosis is reasonably good, with return of visual acuity to normal or near normal in about 50%. The main cause for poor visual acuity is chronic CMO which may lead to secondary RPE changes. To a certain extent prognosis depends on initial visual acuity as follows:

- If initial visual acuity is 6/18 or better, it is likely to remain so.
- If visual acuity is 6/24–6/60, the clinical course is variable, and vision may subsequently improve, remain the same, or worsen.
- If visual acuity at the onset is worse than 6/60, improvement is unlikely.

Management

1. **Follow-up** should be for 3 years to detect conversion to ischaemic CRVO.
2. **Treatment** by high-intensity laser to create an anastomosis between a retinal vein and a choroidal vein, thereby bypassing the site of obstruction to venous outflow, may be beneficial in some cases but is not without potential risks such as fibrous proliferation at the laser site (Fig. 14.60), and haemorrhage from the ruptured vein or from vessels in the choroid. Chronic CMO is unresponsive to laser therapy.

Ischaemic central retinal vein occlusion

Clinical features

1. **Presentation** is with unilateral, sudden and severe visual impairment.
2. **Visual impairment** is profound.
3. **APD** is marked.
4. **Fundus** (Fig. 14.61a)
   - Marked tortuosity and engorgement of all branches of the central retinal vein.
   - Extensive dot-blot and flame-shaped haemorrhages involving the peripheral retina and posterior pole.

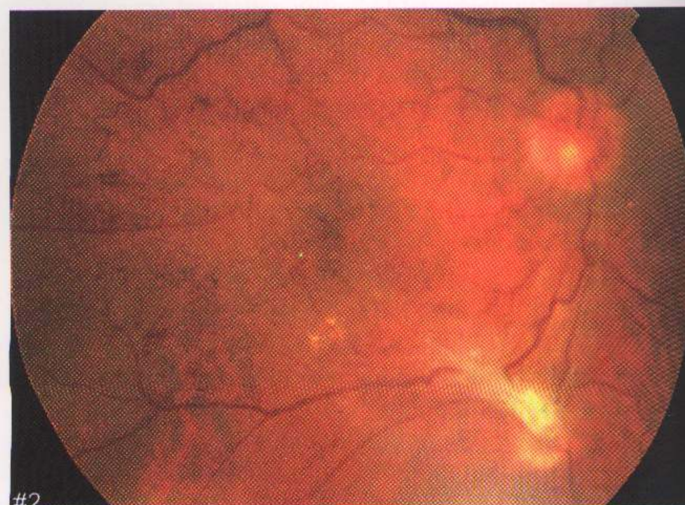


Fig. 14.60
Fibrous proliferation at site of laser-induced anastomosis for non-ischaemic central retinal vein occlusion

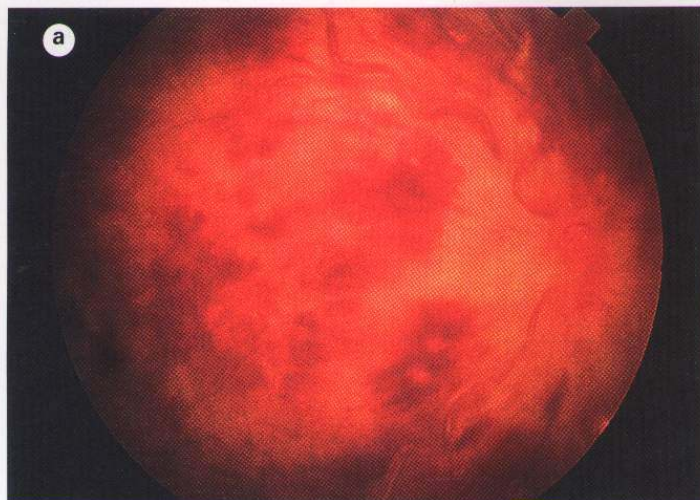




Fig. 14.61
(**a**) Ischaemic central retinal vein occlusion; (**b**) FA showing extensive capillary non-perfusion

- Cotton wool spots, which may be numerous.
- Macular oedema and haemorrhage.
- Severe optic disc oedema and hyperaemia.

5. **FA** shows central masking by retinal haemorrhages and extensive areas of capillary non-perfusion (Fig. 14.61b).
6. **Course**. Most acute signs resolve over the next 9–12 months. Residual findings include disc collaterals, macular epiretinal gliosis and pigmentary changes. Rarely subretinal fibrosis resembling that associated with exudative age-related macular degeneration may develop.
7. **Prognosis** is extremely poor due to macular ischaemia. Rubeosis iridis develops in about 50% of eyes, usually between 2 and 4 months (100-day glaucoma), and unless treated vigorously with PRP there is a high risk of neovascular glaucoma (*see* Chapter 9).

Management

1. **Follow-up** should be monthly for 6 months in order to detect anterior segment neovascularization. Angle neovascularization, while not synonymous with eventual neovascular glaucoma, is the best clinical predictor of the eventual risk of neovascular glaucoma because it may occur in the absence of neovascularization at the pupillary margin.

> *NB:* Routine gonioscopy of eyes at risk should therefore be performed; mere slit-lamp examination of the iris is inadequate.

2. **Treatment**. PRP (Fig. 14.62) should be performed without delay in eyes with angle or iris neovascularization. Prophylactic laser therapy is appropriate only if regular follow-up is not possible. Unfortunately, retinal haemorrhages often have not cleared sufficiently by the time photocoagulation becomes necessary.

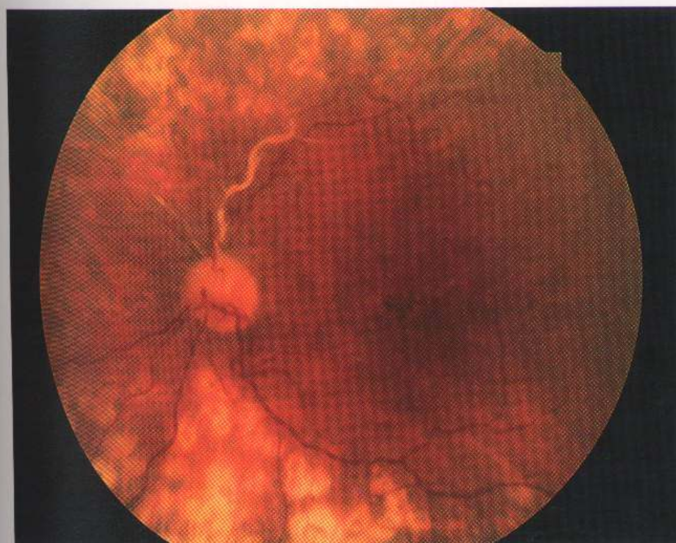


Fig. 14.62
Appearance following laser panretinal photocoagulation for early rubeosis associated with ischaemic central retinal vein occlusion

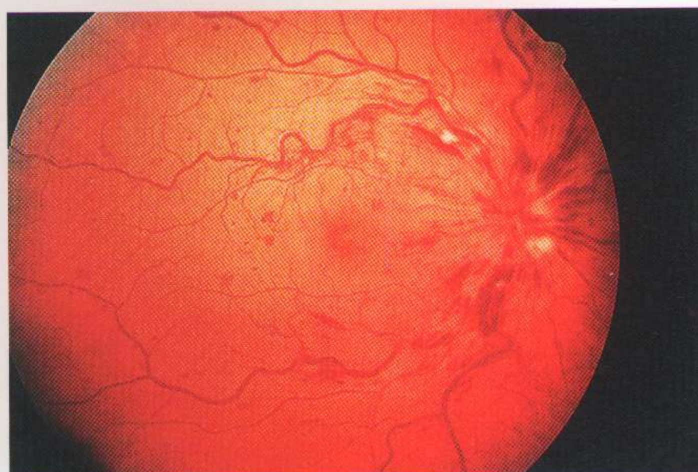


Fig. 14.63
Papillophlebitis

Papillophlebitis

Papillophlebitis (optic disc vasculitis), is an uncommon condition which typically affects otherwise healthy individuals under the age of 50 years. It is thought that the underlying lesion is optic disc swelling with resultant secondary venous congestion rather than venous thrombosis occurring at the level of the lamina cribrosa as occurs in older patients.

1. **Presentation** is with relatively mild blurring of vision typically worst on waking.
2. **Visual impairment** is mild to moderate.
3. **APD** is absent.
4. **Fundus** (Fig. 14.63)
   - Disc oedema, which may be associated with cotton wool spots, is the dominant finding.
   - Venous dilatation and tortuosity with variable amount of retinal haemorrhages, usually confined to the parapapillary area and posterior fundus.
5. **Blind spot** is enlarged.
6. **FA** shows delay in venous filling, hyperfluorescence due to leakage and good capillary perfusion.
7. **Prognosis** is excellent despite the lack of treatment. Eighty per cent of cases achieve a final visual acuity of 6/12 or better. The remainder suffer significant and permanent visual impairment as a result of macular oedema.

Hemiretinal vein occlusion

Hemiretinal vein occlusion is less common than both BRVO and CRVO. It involves occlusion of the superior or inferior branch of the CRV.

1. **Classification**
   a. Hemisphere occlusion of a major branch of the CRV at or near the optic disc.
   b. Hemicentral occlusion, which is less common, involves one trunk of a dual-trunked CRV, which persists in the anterior part of the optic nerve head as a congenital variant.

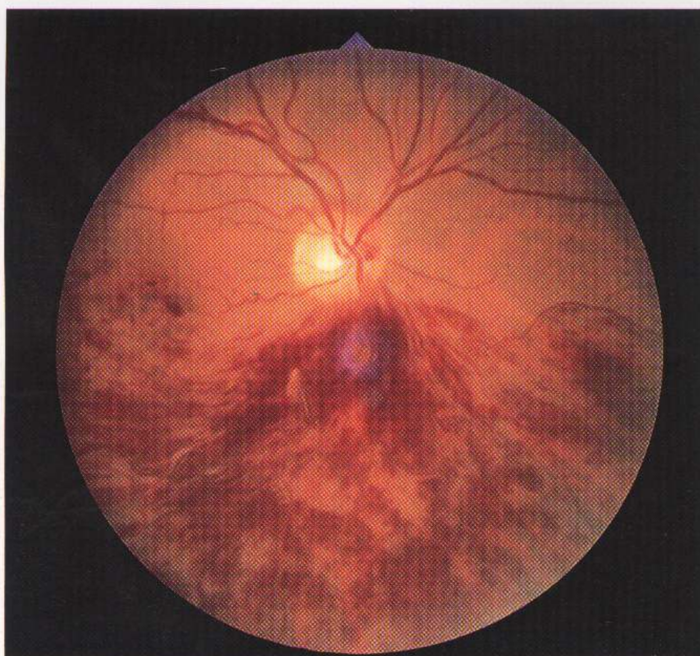


Fig. 14.64
Inferior hemiretinal vein occlusion

2. **Presentation** is with a sudden altitudinal visual field defect.
3. **Visual impairment** is variable.
4. **Fundus**. This shows the features of BRVO, involving the superior or inferior hemisphere (Fig. 14.64).
5. **FA** shows masking by haemorrhages, hyperfluorescence due to leakage and variable retinal capillary non-perfusion.
6. **Prognosis** is dependent on the severity of macular ischaemia and oedema.
7. **Treatment** depends on the severity of retinal ischaemia. Extensive retinal ischaemia carries the risk of neovascular glaucoma and should be managed in the same way as ischaemic CRVO.

Retinal artery occlusion

Introduction

Classification

1. **Branch retinal artery occlusion (BRAO)**.
2. **Central retinal artery occlusion (CRAO)**.
3. **Cilioretinal artery occlusion**.

Causes

1. **Atherosclerosis-related thrombosis** at the level of the lamina cribrosa is by far the most common underlying cause of CRAO, accounting for about 80% of cases.
2. **Carotid embolism** originating from the bifurcation of the common carotid artery. This is a vulnerable site for

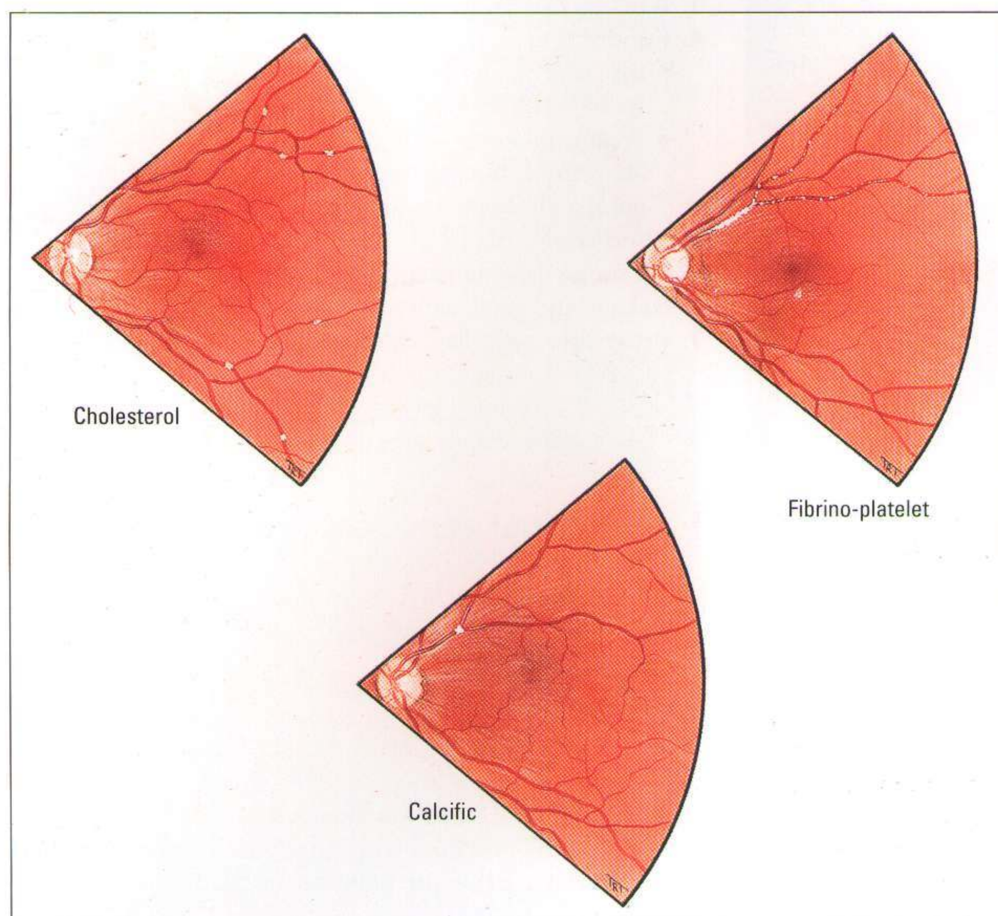
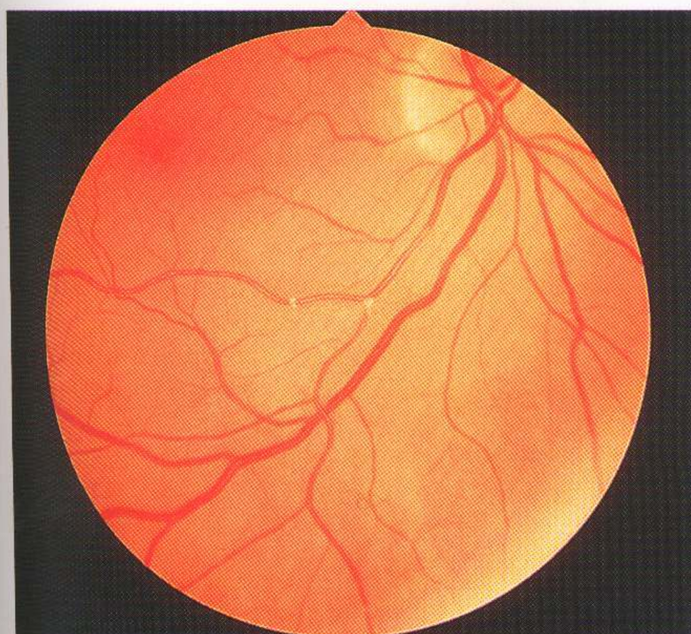


Fig. 14.65
Main types of retinal emboli


Fig. 14.66
Cholesterol emboli (Hollenhorst plaques)

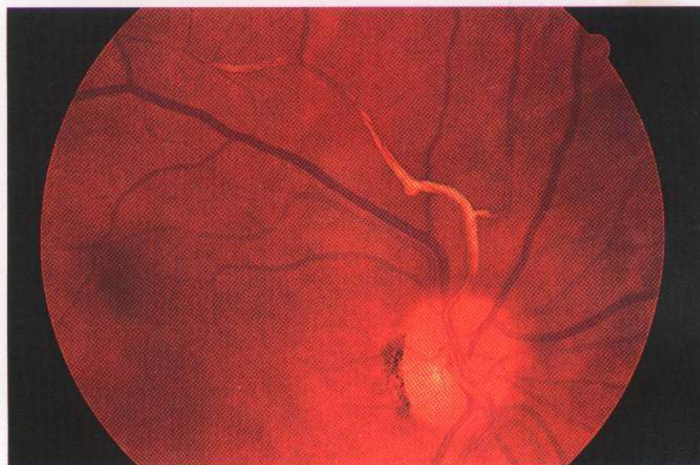
atheromatous ulceration and stenosis (*see* Chapter 20). Retinal emboli from the carotid arteries may be of the following types (Fig. 14.65):

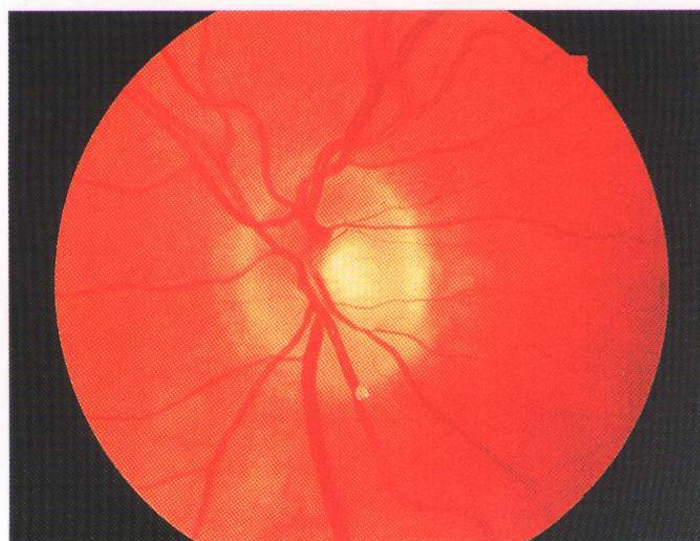
a. ***Cholesterol*** emboli (Hollenhorst plaques) appear as intermittent showers of minute, bright, refractile, golden to yellow-orange crystals, often located at arteriolar bifurcations (Fig. 14.66). They rarely cause significant obstruction to the retinal arterioles and are frequently asymptomatic.

b. ***Fibrinoplatelet*** emboli are dull grey, elongated particles which are usually multiple and occasionally fill the entire lumen (Fig. 14.67). They may cause a retinal transient ischaemic attack (TIA), with resultant amaurosis fugax, and occasionally complete obstruction. Amaurosis fugax is characterized by painless transient unilateral loss of vision, often described as a curtain coming down over the eye, usually from top to bottom, but occasionally vice versa. Visual loss, which may be complete, usually lasts a few minutes. Recovery is in the same pattern as the initial loss, although usually more gradual. Frequency of attacks may vary from several times a day to once every few months. The attacks may be associated with ipsilateral cerebral TIA with contralateral signs.

c. ***Calcific*** emboli may originate from atheromatous plaques in the ascending aorta or carotid arteries, as well as from calcified heart valves. They are usually single, white, non-scintillating and often close to the disc (Fig. 14.68). When located on the disc itself, they may easily be overlooked because they tend to merge with the disc. Calcific emboli are much more dangerous than the other two kinds because they may cause permanent occlusion of the central retinal artery or one of its main branches.

3. **Giant cell arteritis**.
4. **Cardiac embolism** is responsible for about 20% of retinal arterial occlusions and is associated with an increased risk of cerebrovascular disease. Since the ophthalmic artery is the first branch of the internal carotid artery, embolic material from the heart and carotid arteries has a fairly direct route to the eye. Emboli originating from the heart and its valves may be of the following four types:
   a. ***Calcific*** from the aortic or mitral valves.
   b. ***Vegetations*** from cardiac valves in bacterial endocarditis.
   c. ***Thrombus*** from the left side of the heart, consequent to myocardial infarction (mural thrombi), mitral stenosis associated with atrial fibrillation or mitral valve prolapse.
   d. ***Myxomatous material*** from the very rare atrial myxoma.
5. **Periarteritis** associated with dermatomyositis, systemic lupus erythematosus, polyarteritis nodosa, Wegener granulomatosis and Behçet disease may occasionally be responsible for BRAO, which may be multiple (Fig. 14.69).


Fig. 14.67
Fibrinoplatelet emboli


Fig. 14.68
Calcific embolus at the inferior edge of the disc

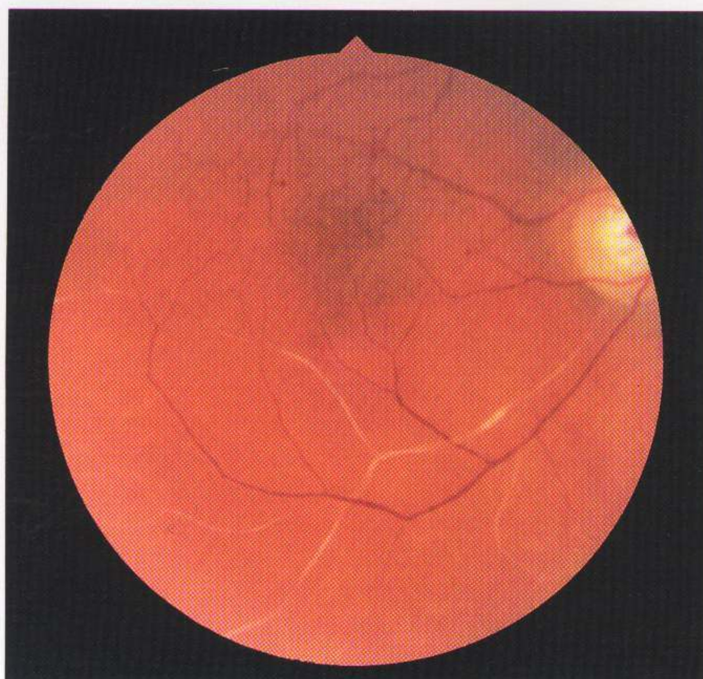


Fig. 14.69
Multiple branch retinal artery occlusions in polyarteritis nodosa

6. **Thrombophilic disorders** such as hyperhomocysteinaemia, antiphospholipid antibody syndrome and inherited defects of natural anticoagulants may occasionally be associated with retinal artery obstruction in young individuals.
7. **Retinal migraine** may very rarely be responsible for retinal artery occlusion in young individuals. However, the diagnosis should be made only after other more common causes have been excluded.

Branch retinal artery occlusion

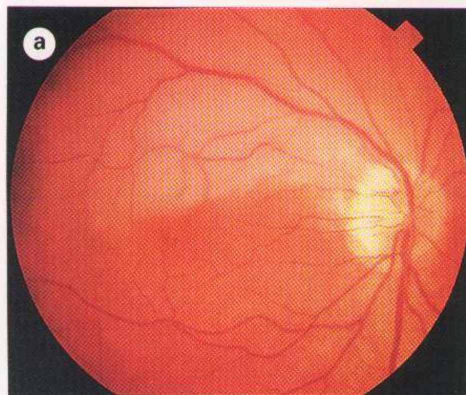
BRAO is most frequently caused by embolism and occasionally by periarteritis.

1. **Presentation** is with sudden and profound altitudinal or sectoral visual field loss.
2. **Visual impairment** is variable.
3. **Fundus** (Fig. 14.70a)
   - Retinal cloudiness corresponding to the area of ischaemia resulting from oedema.
   - Narrowing of arteries and veins with sludging and segmentation of the blood column.
   - One or more emboli may be present.
4. **FA** shows delay in arterial filling and masking of background fluorescence by retinal swelling which is confined to the involved sector (Fig. 14.70b).
5. **Prognosis** is poor unless the obstruction can be relieved within a few hours (*see* below). The visual field defect is permanent and the affected artery remains attenuated. Occasionally, however, recanalization of the obstructed artery may leave subtle or absent ophthalmoscopic signs.

Central retinal artery occlusion

CRAO is most frequently the result of atherosclerosis, although it may also be caused by calcific emboli.

1. **Presentation** is with sudden and profound loss of vision.
2. **Visual impairment** is profound except when a portion of the papillomacular bundle is supplied by a cilioretinal artery, when central vision may be preserved.
3. **APD** is profound or total (amaurotic pupil).
4. **Fundus**
   - Attenuation of arteries and veins with sludging and segmentation of the blood column (cattle-trucking) (Fig. 14.71).
   - Extensive retinal cloudiness (Fig. 14.72).
   - The orange reflex from the intact choroid stands out at the thin foveola, in contrast to the surrounding pale retina, giving rise to the 'cherry-red spot' appearance (Fig. 14.73).
   - In eyes with a cilioretinal artery part of the macula will remain of normal colour (Fig. 14.74a).
5. **FA** shows delay in arterial filling and masking of background choroidal fluorescence by retinal swelling. However, a patent cilioretinal artery will fill during the early phase (Fig. 14.74b).
6. **Prognosis** is poor due to retinal infarction. After a few weeks the retinal cloudiness and the 'cherry-red spot' disappear although the arteries remain attenuated



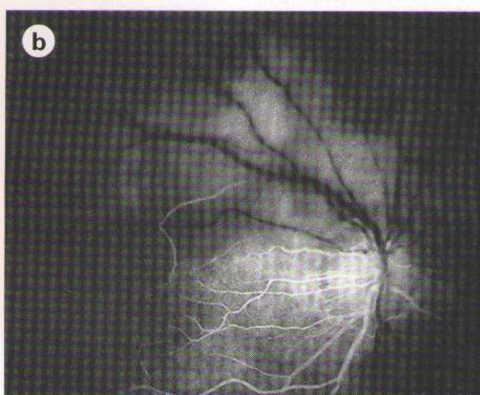


Fig. 14.70
(a) Superotemporal branch retinal artery occlusion; **(b)** FA showing hypofluorescence of the involved sector due to absence of arterial filling and blockage of background fluorescence by oedema (Courtesy of S. Milewski)

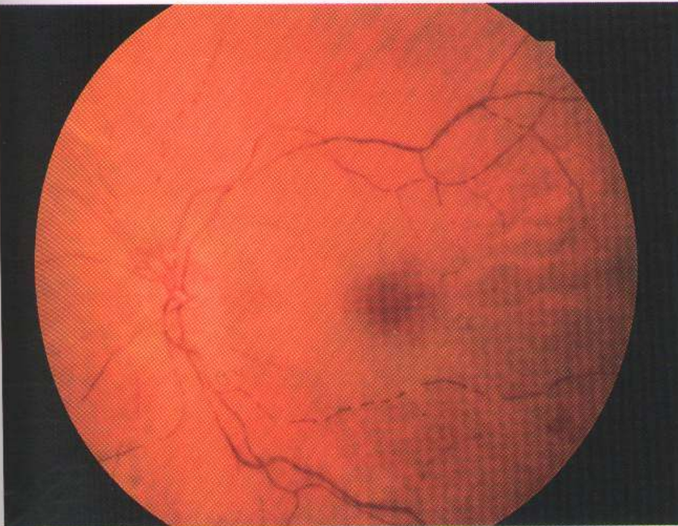


Fig. 14.71
Acute central retinal artery occlusion showing vascular attenuation and segmentation of the blood column (cattle-trucking)

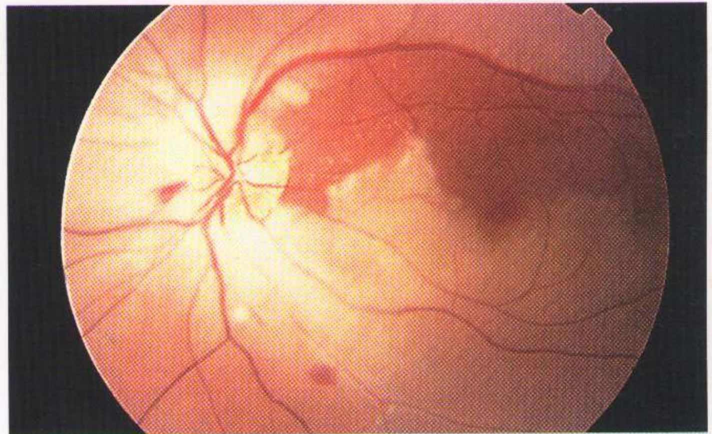


Fig. 14.72
Severe retinal clouding in acute central retinal artery occlusion with sparing of the territory supplied by a cilioretinal artery

(Fig. 14.75). The inner retinal layers become atrophic and consecutive optic atrophy ensures permanent loss of all useful vision. Some eyes develop rubeosis iridis which may require PRP, and about 2% develop NVD.

Cilioretinal artery occlusion

A cilioretinal artery, present in 20% of the population, arises from the posterior ciliary circulation but supplies the retina, commonly in the area of the macula and papillomacular bundle.

1. Classification

a. ***Isolated*** (Fig. 14.76) typically affects young patients with an associated systemic vasculitis.

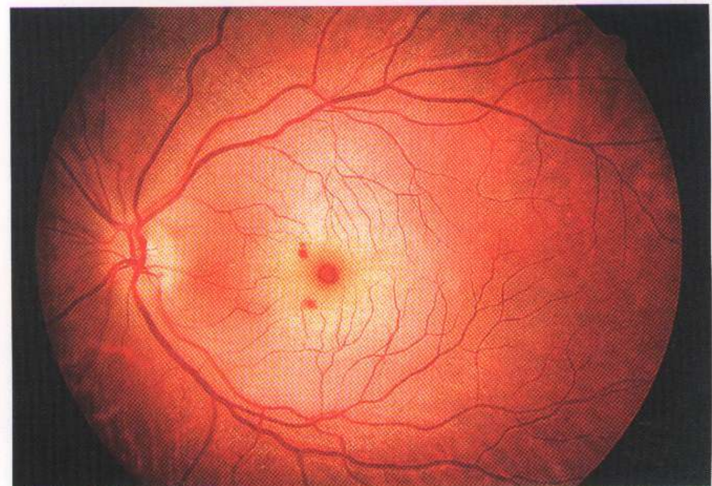
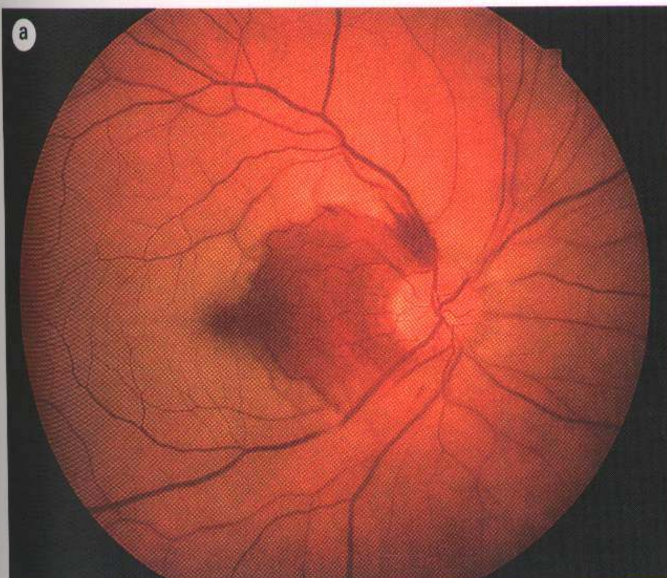


Fig. 14.73
Cherry-red spot at the foveola in acute central retinal artery occlusion (Courtesy of C. Barry)



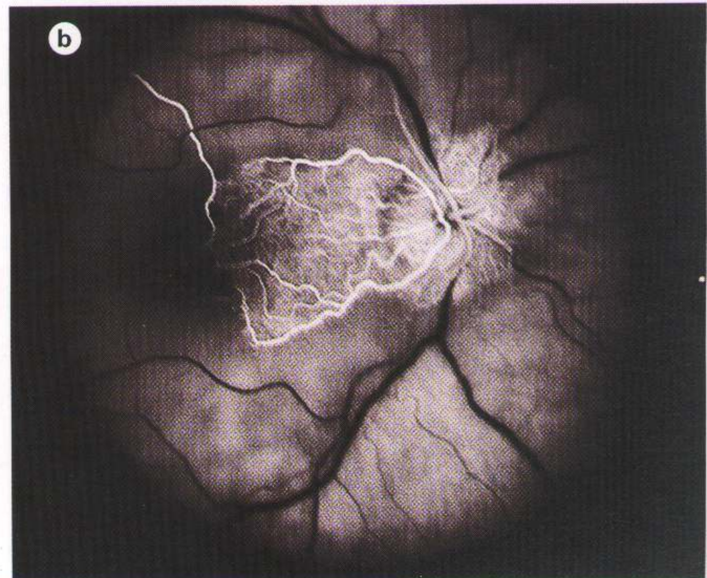


Fig. 14.74
(a) Acute central retinal artery occlusion with sparing of a cilioretinal artery; (**b**) FA showing perfusion only of the macula

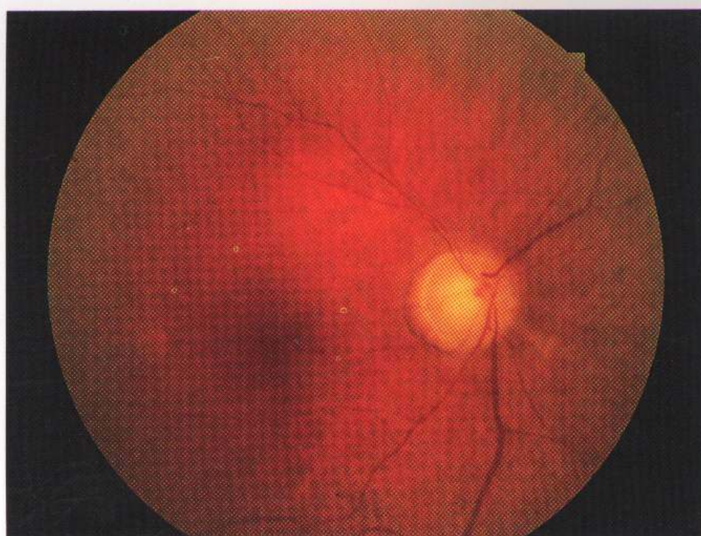


Fig. 14.75
Vascular attenuation and consecutive optic atrophy following central retinal artery occlusion

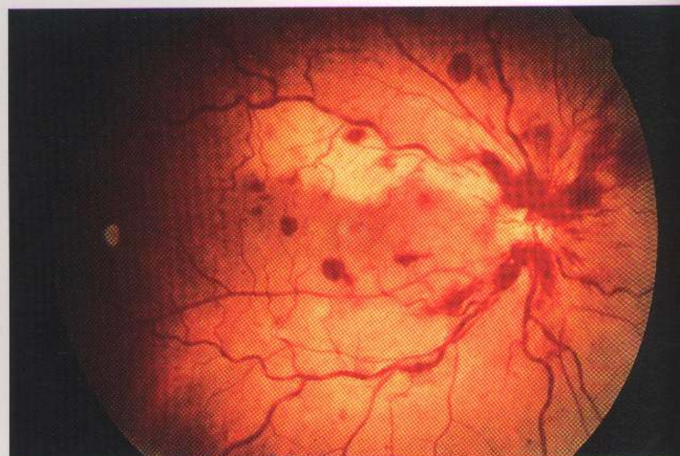


Fig. 14.77
Combined cilioretinal artery and central retinal vein occlusion

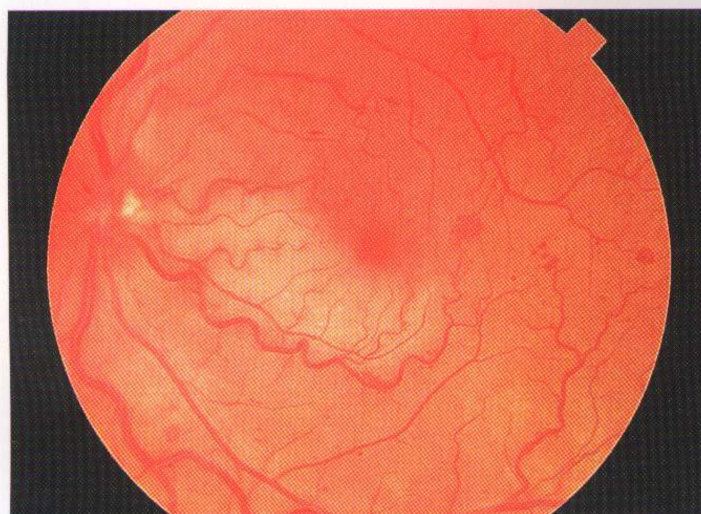


Fig. 14.76
Isolated cilioretinal artery occlusion (Courtesy of S. Milewski)

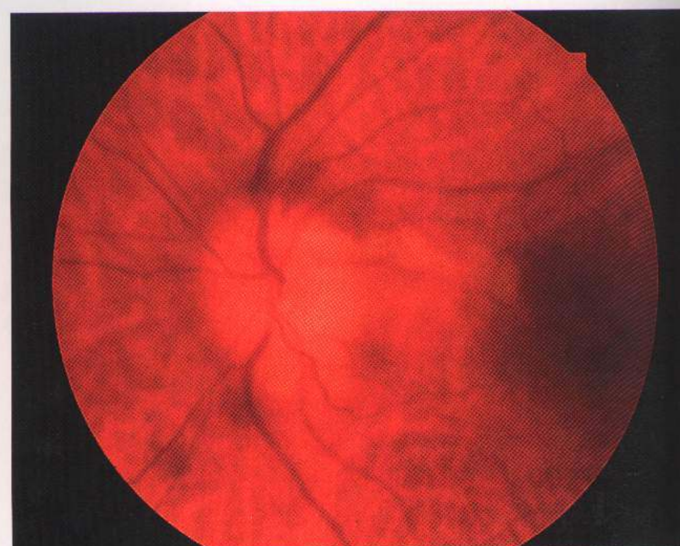


Fig. 14.78
Combined cilioretinal artery occlusion and anterior ischaemic optic neuropathy

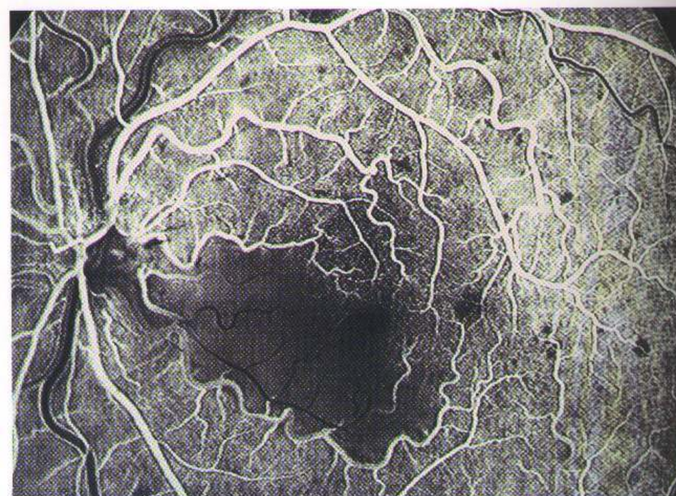


Fig. 14.79
FA of isolated cilioretinal artery occlusion showing hypofluorescence at the macula due to lack of filling and blockage of background choroidal fluorescence (Courtesy of S. Milewski)

   b. ***Combined with CRVO*** (Fig. 14.77) has a similar prognosis to non-ischaemic CRVO.
   c. ***Combined with anterior ischaemic optic neuropathy*** (Fig. 14.78) typically affects patients with giant cell arteritis and carries a very poor prognosis.
2. **Presentation** is with acute, severe loss of central vision.
3. **Fundus**. Cloudiness localized to that part of the retina normally perfused by the vessel.
4. **FA** shows a corresponding filling defect (Fig. 14.79).

Treatment of acute retinal artery occlusion

Retinal artery occlusion is an emergency because it causes irreversible visual loss unless the retinal circulation is re-established prior to the development of retinal infarction. It appears that the prognosis for occlusions caused by calcific

emboli is worse than that resulting from either cholesterol or platelet emboli. Theoretically, timely dislodgement of emboli of the latter two types may prevent subsequent visual loss. To this end many mechanical and pharmacological methods have been tried. The following aggressive systematic stepwise approach gives the greatest chance of success in patients with occlusions of less than 48 hours duration at presentation.

Initial treatment

1. **Ocular massage** using a three-mirror contact lens for approximately 10 seconds, to obtain central retinal artery pulsation or cessation of flow (for BRAO), followed by 5 seconds of release. The aim is to mechanically collapse the arterial lumen and cause prompt changes in arterial flow.
2. **Sublingual isosorbide dinitrate** 10 mg to dilate peripheral blood vessels and decrease resistance.
3. **Lowering of intraocular pressure** with a combination of intravenous acetazolamide 500 mg, followed by intravenous mannitol 20% (1 g/kg) or oral glycerol 50% (1 g/kg).

Subsequent treatment

If the aforementioned measures are unsuccessful in re-establishing circulation after 20 minutes, subsequent treatment is as follows:

1. **Anterior chamber paracentesis**.
2. **Intravenous streptokinase** 750,000 units to disintegrate fibrin emboli, combined with intravenous methylprednisolone 500 mg to decrease the risk of streptokinase-related allergy and bleeding.
3. **Retrobulbar injection** of tolazoline 50 mg to decrease retrobulbar resistance to flow.

Ocular ischaemic syndrome

Pathogenesis

Ocular ischaemic syndrome is an uncommon condition which is the result of chronic ocular hypoperfusion secondary to severe ipsilateral atherosclerotic carotid stenosis. It typically affects patients during the seventh decade and may be associated with diabetes, hypertension, ischaemic heart disease and cerebrovascular disease. The 5-year mortality is of the order of 40%, most frequently from cardiac disease. Patients with ocular ischaemic syndrome may also give a history of amaurosis fugax due to retinal embolism.

Clinical features

The ocular ischaemic syndrome is unilateral in 80% of cases and affects both anterior and posterior segments. The signs are variable and may be subtle, so that the condition may be either missed or misdiagnosed.

1. **Presentation** is usually with gradual loss of vision over several weeks or months although occasionally visual loss may be sudden.
2. **Anterior segment**
   - Diffuse episcleral injection.
   - Corneal oedema and striae.
   - Aqueous flare with few if any cells (ischaemic pseudo-iritis).
   - Mid-dilated and poorly reacting pupil.
   - Iris atrophy.
   - Rubeosis iridis is common and often progresses to neovascular glaucoma.
   - Cataract in very advanced cases.
3. **Fundus**. (Fig. 14.80)
   - Venous dilatation, with or without mild tortuosity, and arteriolar narrowing.
   - Microaneurysms, dot and blot haemorrhages and occasionally cotton wool spots.
   - Proliferative retinopathy with NVD and occasionally NVE.
   - Macular oedema.
   - Spontaneous arterial pulsation most pronounced near the optic disc is present in most cases or may be easily induced by exerting gentle pressure on the globe (digital ophthalmodynamometry).
4. **FA** shows delayed and patchy choroidal filling, prolonged arteriovenous transit time, retinal capillary non-perfusion, late leakage and prominent arterial staining.

Management

1. **Anterior segment manifestations** are treated with topical steroids and mydriatics.
2. **Neovascular glaucoma** may be treated medically or surgically (*see* Chapter 9).

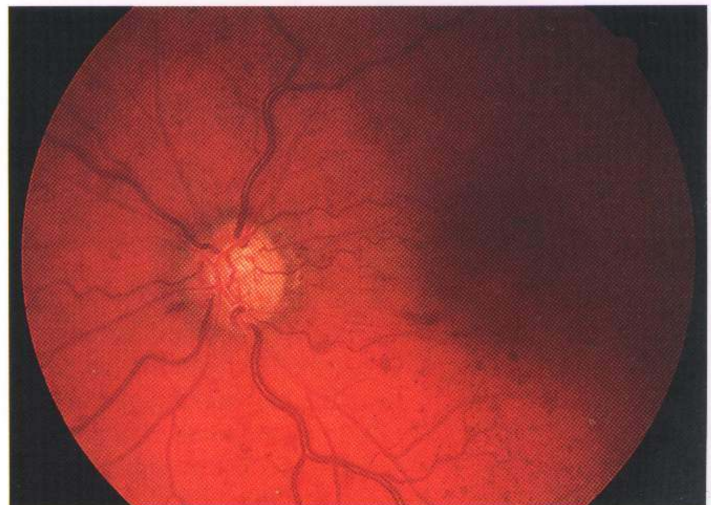


Fig. 14.80
Arteriolar attenuation, venous dilatation, haemorrhages and NVD in ocular ischaemic syndrome

3. **Proliferative retinopathy** requires PRP although the results are less favourable than in proliferative diabetic retinopathy.

Differential diagnosis

1. **Non-ischaemic CRVO**
   - Similarities: unilateral retinal haemorrhages, venous dilatation and cotton wool spots.
   - Differences: normal retinal artery perfusion, haemorrhages are more numerous and mainly flame-shaped, disc oedema is present.
2. **Diabetic retinopathy**
   - Similarities: dot and blot retinal haemorrhages, venous tortuosity and proliferative retinopathy.
   - Differences: usually bilateral and hard exudates are present.
3. **Hypertensive retinopathy**
   - Similarities: arteriolar attenuation and focal constriction, haemorrhages and cotton wool spots.
   - Differences: invariably bilateral and absence of venous changes.

Hypertensive retinopathy

Systemic hypertension is diagnosed on blood pressure readings on several consecutive occasions of 140/90 or over (*see* Chapter 20).

Retinal changes

The primary response of the retinal arterioles to systemic hypertension is narrowing (vasoconstriction). However, the degree of narrowing is dependent on the amount of pre-existing replacement fibrosis (involutional sclerosis). For this reason, hypertensive narrowing is seen in its pure form only in young individuals. In older patients, rigidity of retinal arterioles due to involutional sclerosis prevents the same degree of narrowing seen in young individuals. In sustained hypertension the inner blood–retinal barrier is disrupted in small areas, with increased vascular permeability. The fundus picture of hypertensive retinopathy is therefore characterized by the following:

1. **Arterial narrowing** may be focal (Fig. 14.81) or generalized (Fig. 14.82). Ophthalmoscopic diagnosis of generalized narrowing is difficult, although the presence of focal narrowing makes it highly probable that blood pressure is raised. Severe hypertension may lead to obstruction of the precapillary arterioles and the development of cotton wool spots (Fig. 14.83).
2. **Vascular leakage** leads to flame-shaped retinal haemorrhages and retinal oedema (Fig. 14.84). Chronic retinal oedema may result in the deposition of hard exudates around the fovea in Henle layer with a macular star configuration (Fig. 14.85). Swelling of the optic nerve head is the hallmark of malignant hypertension (Fig. 14.86).

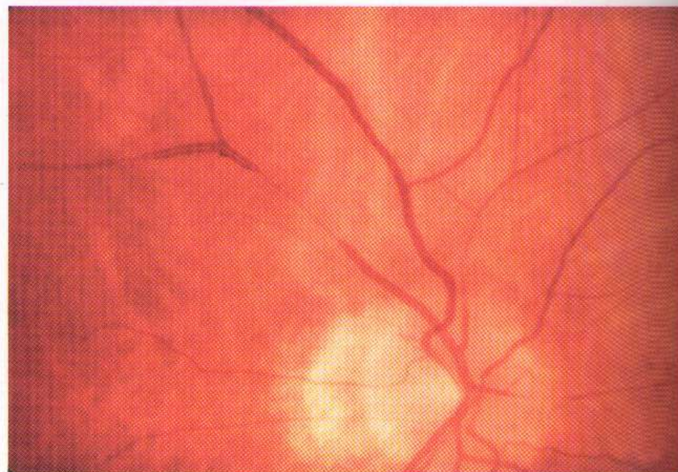


Fig. 14.81
Focal arterial narrowing in hypertension



Fig. 14.82
Generalized arterial narrowing in hypertension

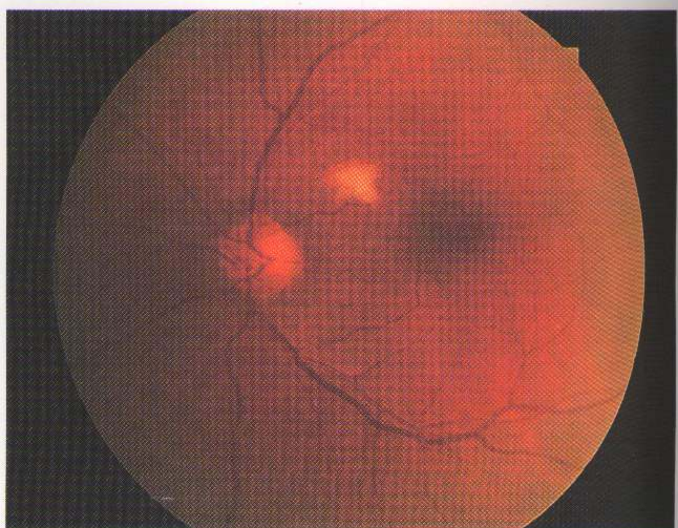


Fig. 14.83
Arterial narrowing and a cotton wool spot in hypertension

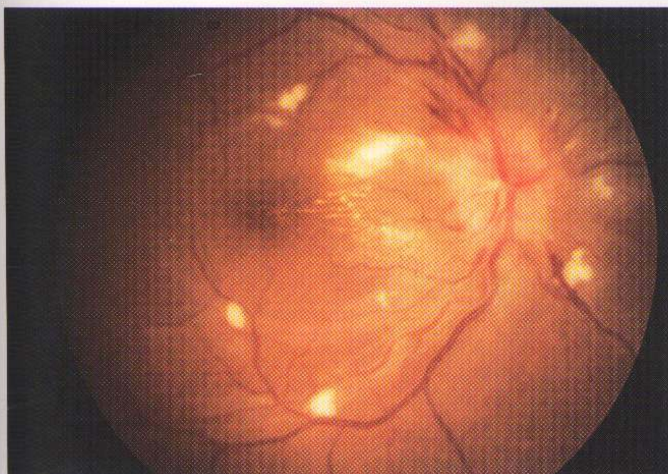


Fig. 14.84
Severe hypertensive retinopathy with cotton wool spots, flame-shaped haemorrhages, early macular star formation and mild disc swelling

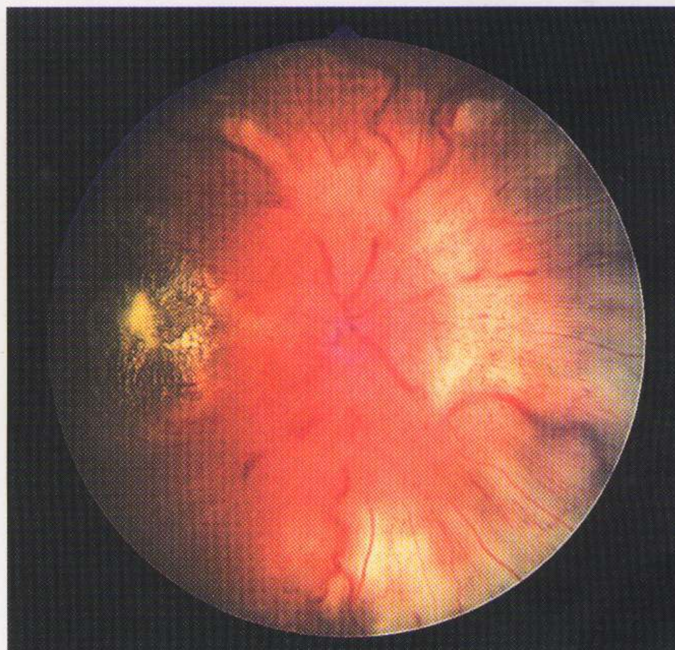


Fig. 14.86
Very severe hypertensive retinopathy with severe disc oedema and a macular star

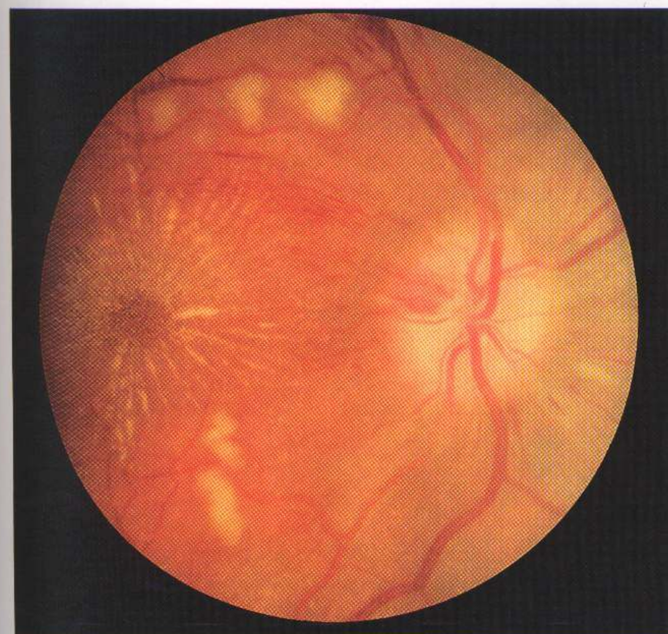


Fig. 14.85
Severe hypertensive retinopathy with a fully developed macular star, cotton wool spots, a few flame-shaped haemorrhages and moderate disc swelling

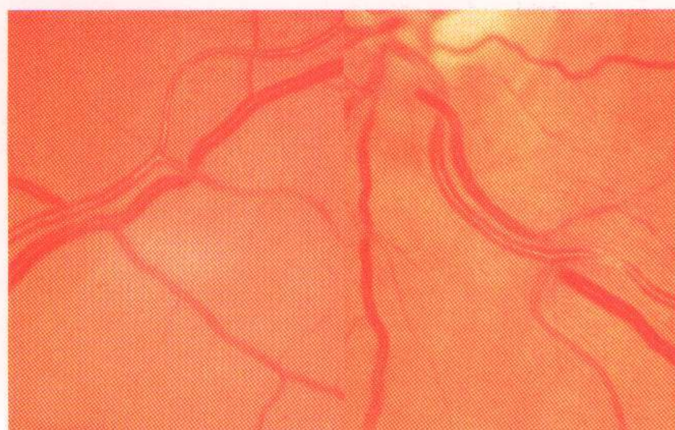


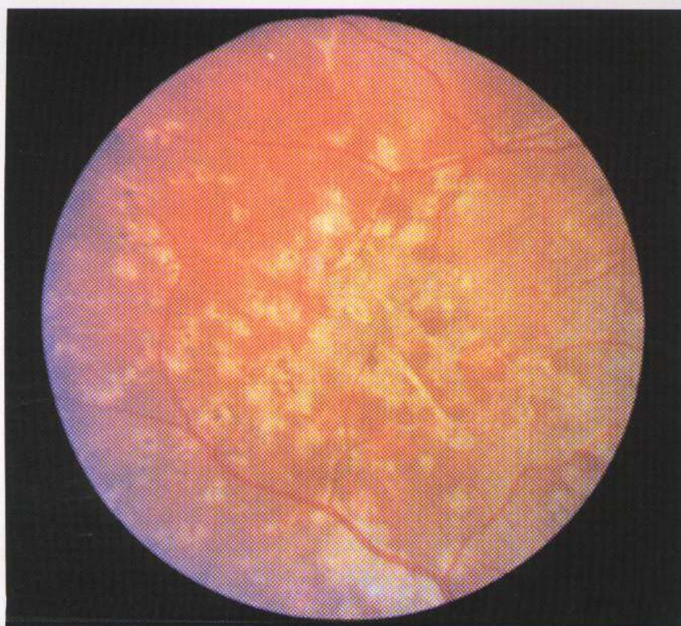
Fig. 14.87
Hypertensive changes at arteriovenous crossings

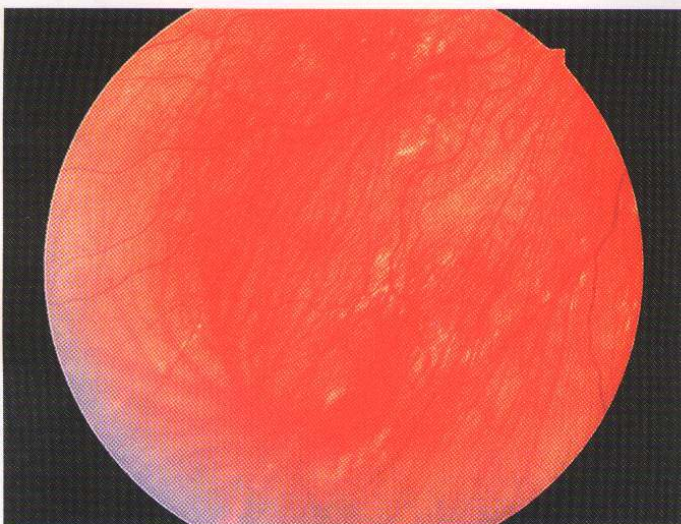
3. **Arteriolosclerosis** involves thickening of the vessel wall characterized histologically by intimal hyalinization, medial hypertrophy and endothelial hyperplasia. The most important clinical sign is the presence of changes at arteriovenous crossings (AV nipping) (Fig. 14.87), which although not necessarily indicative of the severity of hypertension, makes it probable that it has been present for many years. Mild changes at arteriovenous crossings are seen in patients with involutional sclerosis in the absence of hypertension. The grading of arteriolosclerosis is shown in Fig. 14.90.

Choroidal changes

These are rare but may occur as the result of an acute hypertensive crisis (accelerated hypertension) in young adults.

1. **Elschnig spots** are small, black spots surrounded by yellow haloes (Fig. 14.88) which represent focal choroidal infarcts.
2. **Siegrist streaks** are flecks arranged linearly along choroidal vessels (Fig. 14.89) which are indicative of fibrinoid necrosis associated with malignant hypertension.
3. **Exudative retinal detachment**, sometimes bilateral, may occur in severe acute hypertension such as that associated with toxaemia of pregnancy.


Fig. 14.88
Elschnig spots in hypertension


Fig. 14.89
Siegrist lines in hypertenion

Grading of arteriolosclerosis (Fig. 14.90)

1. **Grade 1**. Subtle broadening of the arteriolar light reflex, mild generalized arteriolar attenuation, particularly of small branches, and vein concealment.
2. **Grade 2**. Obvious broadening of the arteriolar light reflex and deflection of veins at arteriovenous crossings (Salus sign).
3. **Grade 3**. Copper-wiring of arterioles, banking of veins distal to arteriovenous crossings (Bonnet sign), tapering of veins on either side of the crossings (Gunn sign) and right-angled deflection of veins.
4. **Grade 4**. Silver-wiring of arterioles and grade 3 changes.

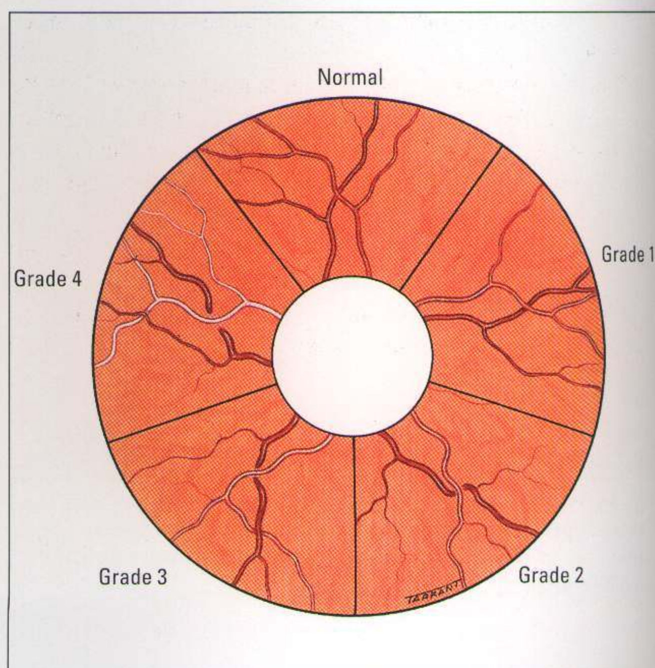


Fig. 14.90
Grading of retinal arteriolosclerosis (*see text*)

Ocular associations and complications of hypertension

- Retinal vein occlusion.
- Retinal artery occlusion.
- Retinal artery macroaneurysm.
- Anterior ischaemic optic neuropathy.
- Ocular motor nerve palsy.
- Uncontrolled hypertension may adversely affect diabetic retinopathy.

Sickle-cell retinopathy

Introduction

Sickling haemoglobinopathies are caused by one, or a combination, of abnormal haemoglobins which cause the red blood cell to adopt an anomalous shape under conditions of hypoxia and acidosis. Because these deformed red blood cells are more rigid than healthy cells, they may become impacted in and obstruct small blood vessels, causing tissue ischaemia with a marked local increase in acidosis and hypoxia, and even more sickling. The sickling disorders in which the mutant haemoglobins S and C are inherited as alleles of normal haemoglobin A have important ocular manifestations. These abnormal haemoglobins may occur in combination with normal haemoglobin A or in association with each other as indicated below:

1. **AS** (sickle-cell trait) is present in 8% of African Americans. It is the mildest form and usually requires

severe hypoxia or other abnormal conditions to produce sickling.

2. **SS** (sickle-cell disease, sickle-cell anaemia) is present in 0.4% of African Americans. It causes severe systemic complications, such as painful infarctive crises and severe haemolytic anaemia. Ocular complications are usually mild and asymptomatic.
3. **SC** (sickle-cell C disease) is present in 0.2% of African Americans.
4. **SThal** (sickle-cell thalassaemia); both SC and SThal are associated with mild anaemia but severe ocular manifestations.

Proliferative retinopathy

Although the most severe forms of retinopathy are associated with SC and SThal diseases, SS may occasionally also cause retinopathy.

Clinical features

1. **Staging** (Fig. 14.91)
   - *Stage 1*. Peripheral arteriolar occlusion.
   - *Stage 2*. Peripheral arteriovenous anastomoses which appear to be dilated pre-existent capillary channels. The peripheral retina beyond the point of vascular occlusion is largely avascular and non-perfused.
   - *Stage 3*. Sprouting of new vessels from the anastomoses. Initially, the new vessels lie flat on the retina, have a 'sea-fan' configuration and are usually fed by a single arteriole and drained by a single vein (Fig. 14.92a). Between 40% and 50% of 'sea-fans' spontaneously involute as a result of auto-infarction and appear as greyish fibrovascular lesions. In other cases the neovascular tufts continue to proliferate, become adherent to the cortical vitreous gel and may bleed as a result of vitreoretinal traction (Fig. 14.93).
   - *Stage 4*. Vitreous haemorrhage which may be precipitated by relatively trivial ocular trauma.
   - *Stage 5*. Extensive fibrovascular proliferation and tractional retinal detachment (Fig. 14.94). Rhegmatogenous retinal detachment may also occur as a result of tear formation adjacent to areas of fibrovascular tissue.
2. **FA** shows extensive capillary non-perfusion of the peripheral retina (*see* Fig. 14.92b) and late leakage from neovascularization (*see* Fig. 14.92c).

Treatment

1. **Peripheral retinal photocoagulation** to areas of capillary non-perfusion may be required to induce regression of neovascular tissue in patients with recurrent vitreous haemorrhages. However, unlike DR, new vessels in sickle cell disease tend to auto-infarct and involute spontaneously without treatment.
2. **Pars plana vitrectomy** for tractional retinal detachment and/or persistent vitreous haemorrhage usually gives poor results.

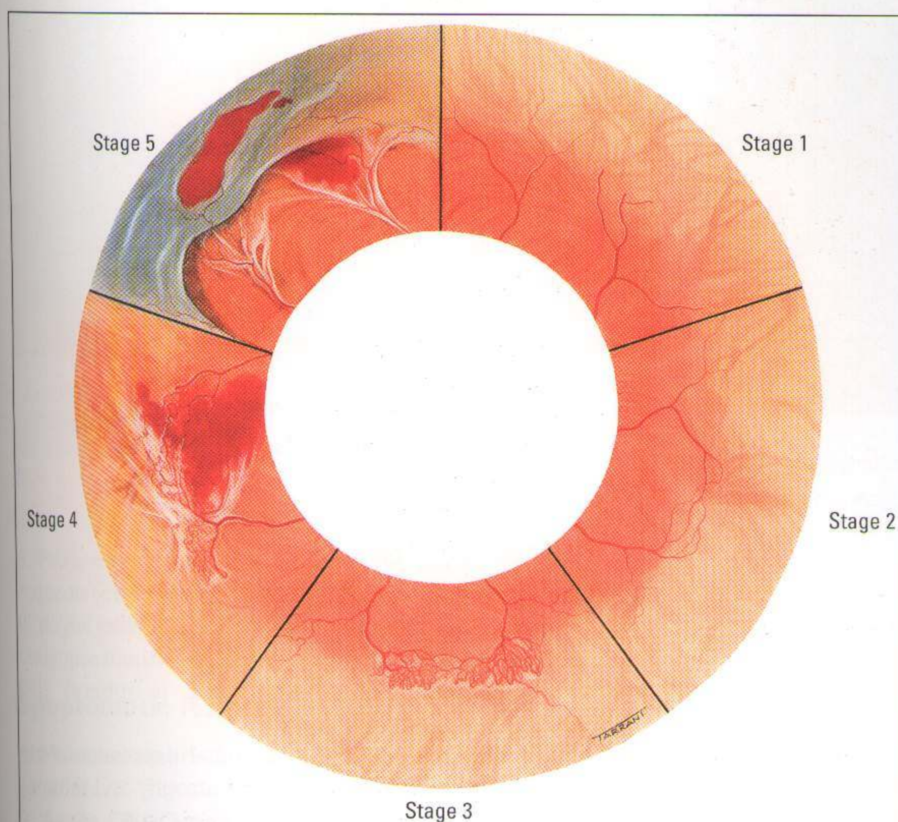


Fig. 14.91
Grading of proliferative sickle-cell retinopathy (*see text*)

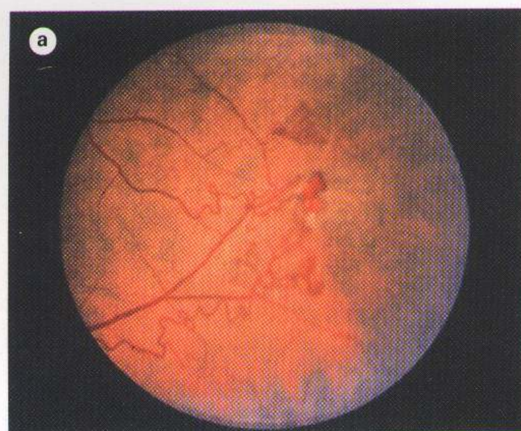
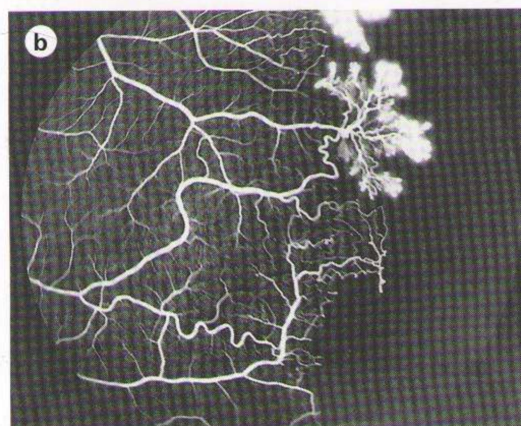
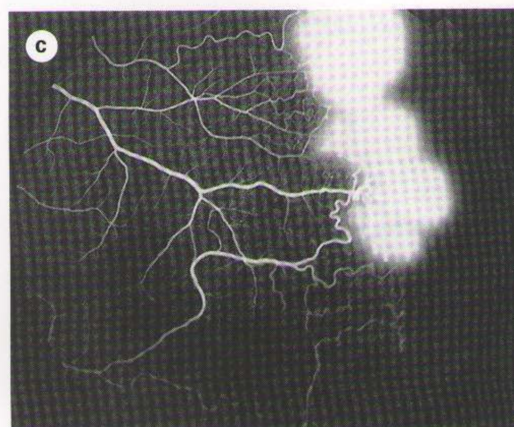


Fig. 14.92
(**a**) Proliferative sickle-cell retinopathy stage 3; (**b**) early FA showing filling of new vessels ('sea-fans') and extensive peripheral retinal capillary non-perfusion; (**c**) late FA showing leakage from new vessels





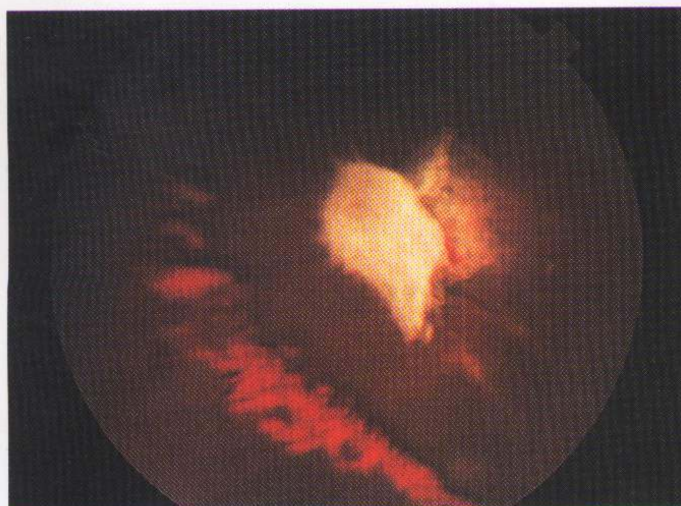


Fig. 14.93
Haemorrhage from new vessels in stage 4 proliferative sickle-cell retinopathy



Fig. 14.94
Peripheral tractional retinal detachment in stage 5 proliferative sickle-cell retinopathy

Non-proliferative retinopathy

Asymptomatic lesions

1. **Venous tortuosity** is one of the first ophthalmic signs of sickling and is due to peripheral arteriovenous shunts.
2. **Silver-wiring of arterioles** in the peripheral retina, which represent previously occluded arterioles.
3. **Salmon patches** are pink, preretinal (Fig. 14.95) or superficial intraretinal haemorrhages at the equator, which lie adjacent to arterioles and usually resolve without sequelae.
4. **Black sunbursts** are patches of peripheral RPE hyperplasia (Fig. 14.96).
5. **Macular depression sign** is an oval depression of the bright central macular reflex due to atrophy and thinning of the sensory retina.

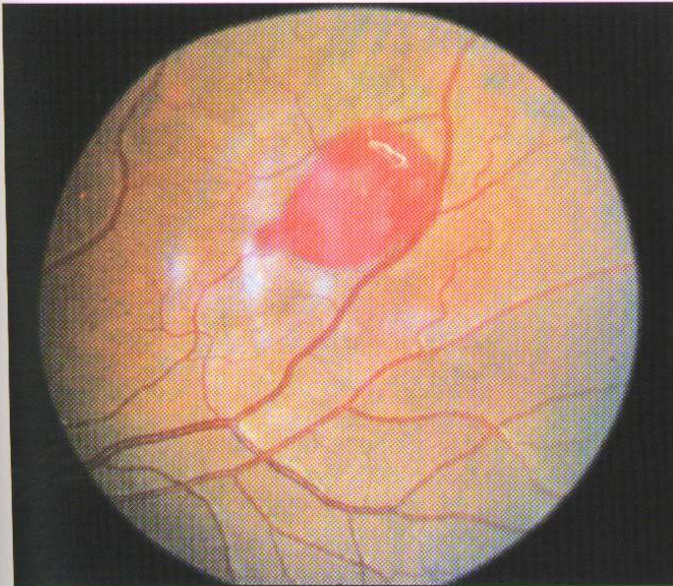


Fig. 14.95
Preretinal haemorrhage (salmon patch) in sickle-cell retinopathy

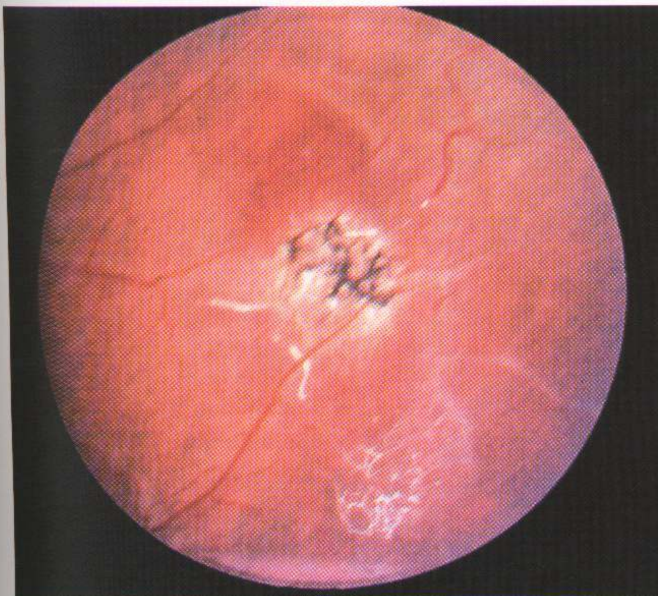


Fig. 14.96
Peripheral RPE hyperplasia (black sunburst) in sickle-cell retinopathy

6. **Peripheral retinal holes** and areas of whitening similar to 'white-without-pressure' are occasionally seen (Fig. 14.97).

Symptomatic lesions

1. **Macular arteriolar occlusion** occurs in about 30% of patients.
2. **Acute CRAO** is rare.

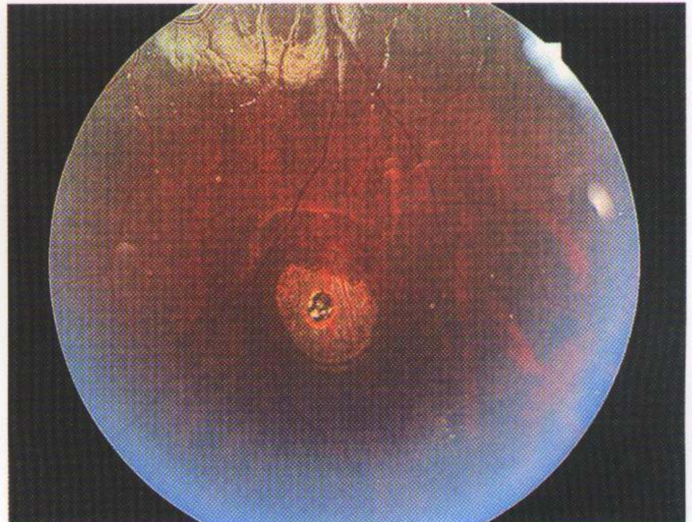


Fig. 14.97
Peripheral retinal hole and an area of whitening superiorly in sickle-cell retinopathy

3. **Retinal vein occlusion**, due to hyperviscosity, is uncommon.
4. **Choroidal vascular occlusion** may be seen occasionally, particularly in children.
5. **Angioid streaks** occur in a minority of patients.

Non-retinal lesions

1. **Conjunctival** lesions are characterized by isolated dark-red vascular anomalies shaped like commas or corkscrews. They involve the small calibre vessels and are most often located inferiorly.
2. **Iris** lesions consist of circumscribed areas of ischaemic atrophy, usually at the pupillary edge and extending to the collarette. Rubeosis may be seen occasionally.

Retinopathy of prematurity

Introduction

Retinopathy of prematurity (ROP) is a proliferative retinopathy affecting pre-term infants of low birth weight who have often been exposed to high ambient oxygen concentrations. The retina is unique among tissues in that it has no blood vessels until the fourth month of gestation, at which time vascular complexes emanating from the hyaloid vessels at the optic disc grow towards the periphery. These vessels reach the nasal periphery after 8 months of gestation, but do not reach the temporal periphery until about 1 month after delivery. The incompletely vascularized temporal retina is particularly susceptible to oxygen damage, especially in the pre-term infant.

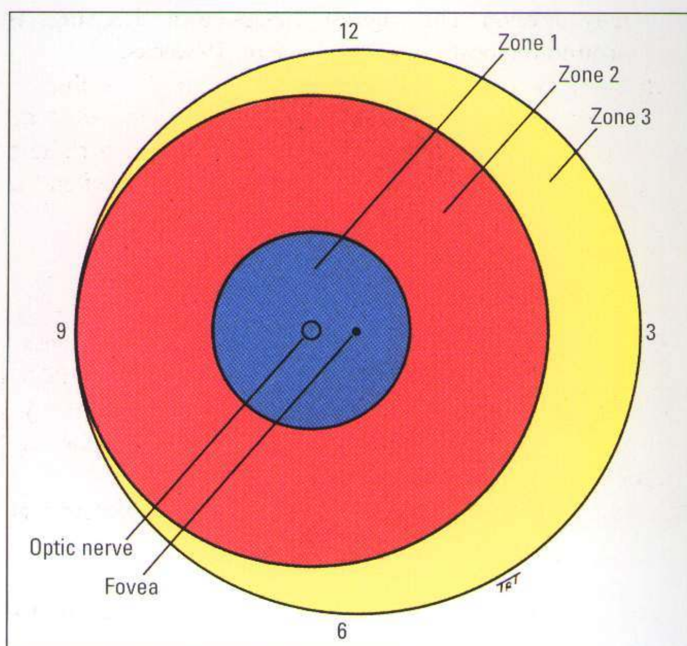


Fig. 14.98
Grading of retinopathy of prematurity (*see text*)

Active ROP

Severity

This is determined in terms of (a) *location*, (b) *extent*, (c) *stages* and (d) *'plus' disease* as follows:

1. **Location** is determined according to three zones centred on the optic disc (Fig. 14.98).
   a. *Zone 1* is bounded by an imaginary circle the radius of which is twice the distance from the disc to the macula.
   b. *Zone 2* extends concentrically from the edge of zone 1 to the nasal ora serrata and to an area near the temporal equator.
   c. *Zone 3* consists of a residual temporal crescent anterior to zone 2.
2. **Extent** of involvement is determined by the number of clock hours of retina involved.
3. **Staging**
   a. *Stage 1* (demarcation line). The first pathognomonic sign of ROP is the development of a thin, tortuous, grey-white line running roughly parallel with the ora serrata which

Demarcation line
Vascularized retina
Avascular retina
a
Ridge
Isolated neovascular tufts
b
c
Severe extraretinal fibrovascular proliferation
d
Detached retina

Fig. 14.99
Progression of retinopathy of prematurity (*see text*)

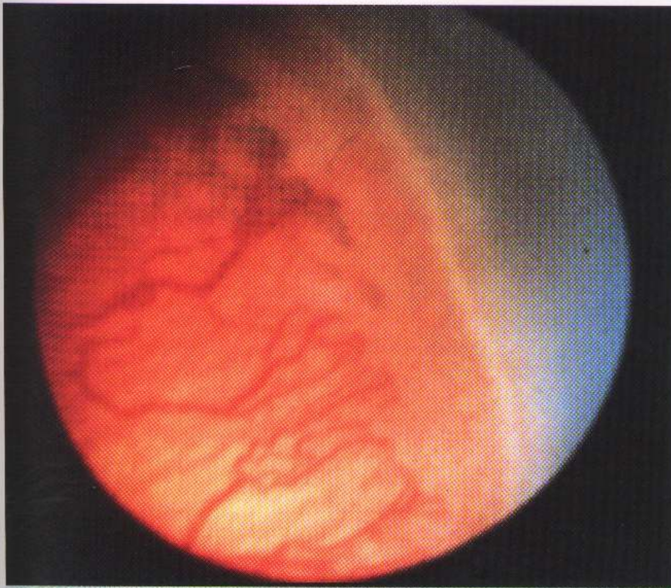


Fig. 14.100
Elevated ridge in retinopathy of prematurity stage 2 (Courtesy of J Arnold)

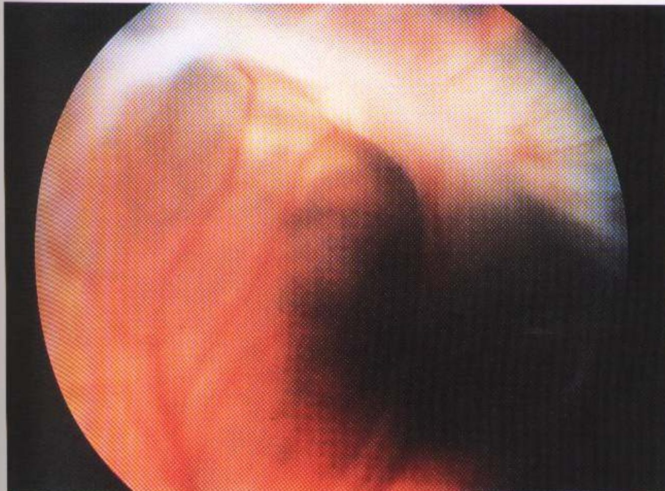


Fig. 14.101
Ridge with extensive fibrovascular proliferation in retinopathy of prematurity stage 3

separates avascular immature peripheral retina from vascularized posterior retina (Fig. 14.99a). The line is more prominent in the temporal periphery and may have abnormal branching blood vessels leading up to it.

b. *Stage 2* (ridge). If ROP progresses the demarcation line develops into an elevated ridge which represents a mesenchymal shunt joining arterioles with veins (Figs 14.99b and 14.100). Blood vessels enter the ridge and small isolated neovascular tufts may be seen posterior to it.

c. *Stage 3* (ridge with extraretinal fibrovascular proliferation). As the disease progresses, the ridge develops a pink colour due to fibrovascular proliferation which grows along the surface of the retina and into the vitreous (Figs 14.99c and 14.101). This is often associated with dilatation and tortuosity of the retinal blood vessels posterior to the equator. Retinal haemorrhage is common, and vitreous haemorrhage may develop. The highest incidence of this stage is around the post-conceptual age of 35 weeks.

d. *Stage 4* (sub-total retinal detachment) is due to progressive fibrovascular proliferation (Fig. 14.99d). The detachment, which starts in the extreme periphery and then spreads centrally, typically develops when the infant is about 10 weeks old.

e. *Stage 5* is a total retinal detachment.

NB: Although the clinical features of ROP usually take several weeks to develop, rarely the disease can progress from stage 1 to stage 4 within a few days. In about 80% of infants, ROP regresses spontaneously, leaving few if any residua. Spontaneous regression may even occur in patients with partial retinal detachments.

Other considerations

1. **Plus disease** signifies a tendency to progression and is characterized by the following:
   - Failure of the pupil to dilate, associated with gross vascular engorgement of the iris.
   - Development of vitreous haze.
   - Dilatation of veins and tortuosity of the arteries in the posterior fundus (Fig. 14.102).
   - Increasing preretinal and vitreous haemorrhage.

   When these changes are present, a plus sign is added to the stage number.
2. **Threshold disease** is defined as five contiguous clock hours or eight non-contiguous clock hours of extraretinal neovascularization (stage 3 disease) in zone 1 or zone 2, associated with plus disease, and is an indication for treatment.

Screening

Babies born at or before 31 weeks gestational age, or weighing 1500 g or less, should be screened for ROP.

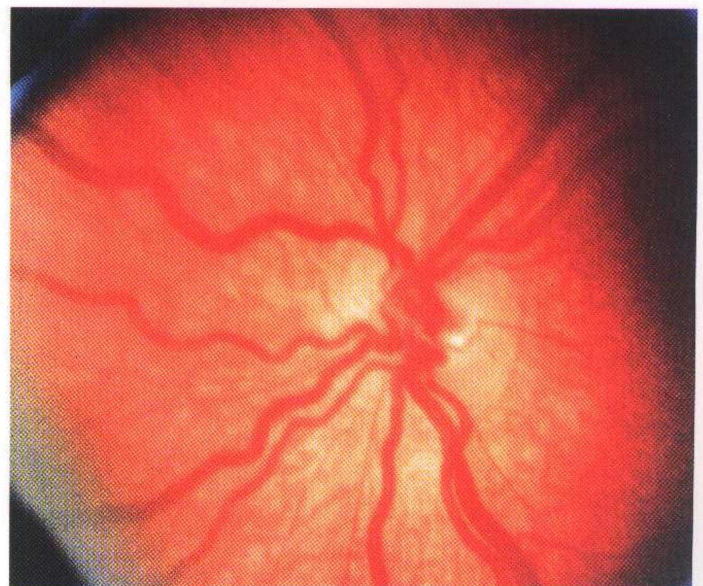


Fig. 14.102
Vascular dilatation in retinopathy of prematurity 'plus' disease

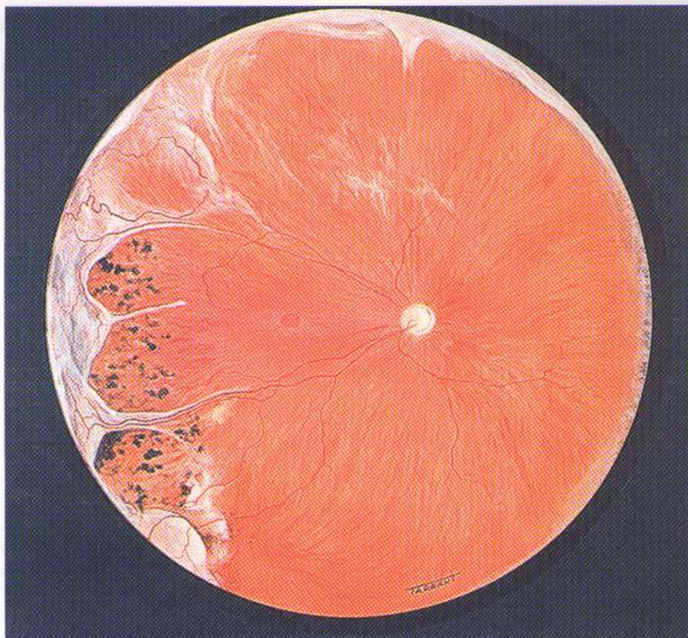


Fig. 14.103
Peripheral fibrous proliferation and pigmentary changes with straightening of temporal blood vessels in cicatricial retinopathy of prematurity

Screening prior to the age of 31 weeks gestational age is, however, often of little value since pupillary dilatation is difficult and visualization of the fundus is impaired by the tunica vasculosa lentis. Screening of premature infants should therefore be between 6 and 7 weeks post-natal age or 34 weeks post-conceptual age (whichever comes first), but not before 5 weeks post-natal age, to detect the onset of threshold disease. Subsequent review should be at 2-weekly intervals, until retinal vascularization reaches zone 3. Other systemic complications, such as intraventricular haemorrhage, may increase the risk of ROP. The pupils in a pre-term infant should be dilated with 0.5% cyclopentolate with or without 2.5% phenylephrine.

Treatment

1. **Ablation** of avascular immature retina by cryotherapy or laser photocoagulation is recommended in infants with threshold disease. This is successful in 85% of cases, but the remainder progress to retinal detachment in spite of treatment.
2. **Vitreoretinal surgery** for tractional retinal detachment usually has a poor visual outcome.

Cicatricial ROP

About 20% of infants with active ROP develop cicatricial complications, which range from innocuous to extremely severe. In general, the more advanced or the more posterior the proliferative disease at the time of involution, the worse the cicatricial sequelae.

- **Stage 1**. Myopia associated with mild peripheral retinal pigmentary disturbance and haze at the vitreous base.
- **Stage 2**. Temporal vitreoretinal fibrosis (Fig. 14.103) with dragging of the macula (Fig. 14.104), which may lead to a pseudo-exotropia, due to resultant exaggeration of angle kappa (*see* Chapter 16).
- **Stage 3**. More severe peripheral fibrosis with contracture and a falciform retinal fold (Fig. 14.105).
- **Stage 4**. Partial ring of retrolental fibrovascular tissue with partial retinal detachment.
- **Stage 5**. Complete ring of retrolental fibrovascular tissue with total retinal detachment (Fig. 14.106), a picture formerly known as 'retrolental fibroplasia'. Secondary angle-closure glaucoma may develop due to progressive

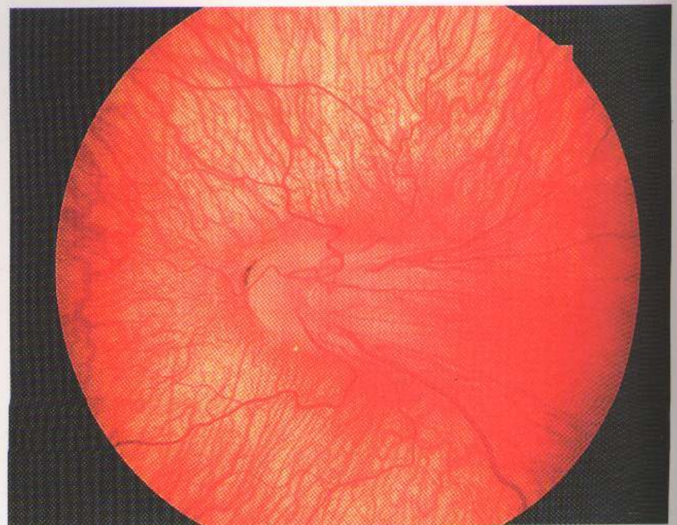


Fig. 14.104
Temporal dragging of the macula in cicatricial retinopathy of prematurity



Fig. 14.105
Falciform vitreoretinal fold with inferotemporal dragging of the retina in cicatricial retinopathy of prematurity

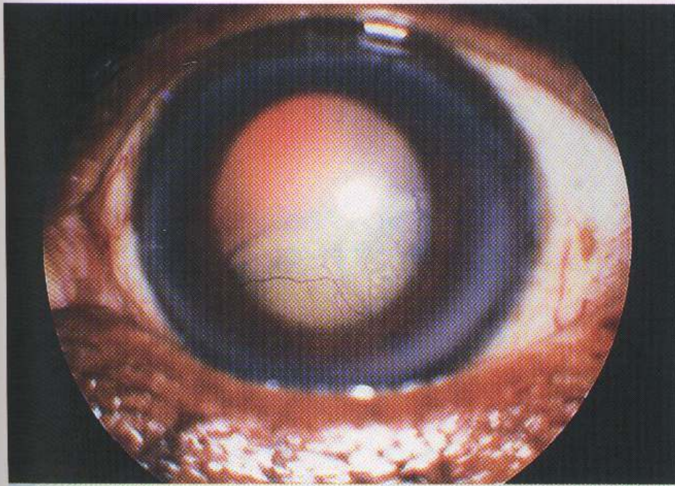


Fig. 14.106
Total retinal detachment in retinopathy of prematurity

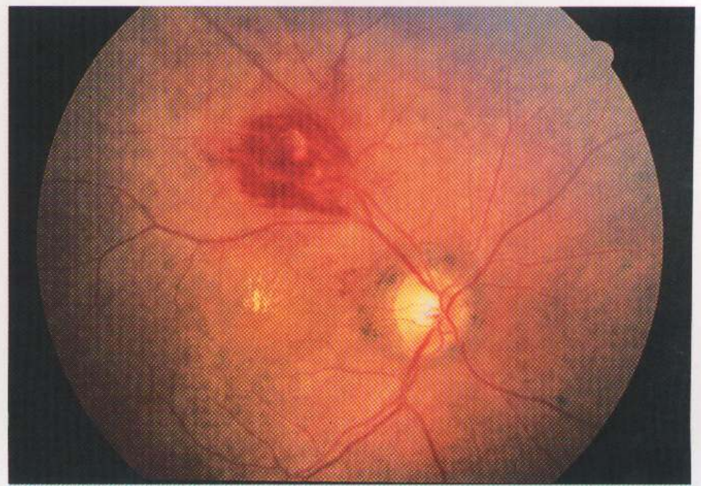


Fig. 14.107
Retinal artery macroaneurysm with localized haemorrhage

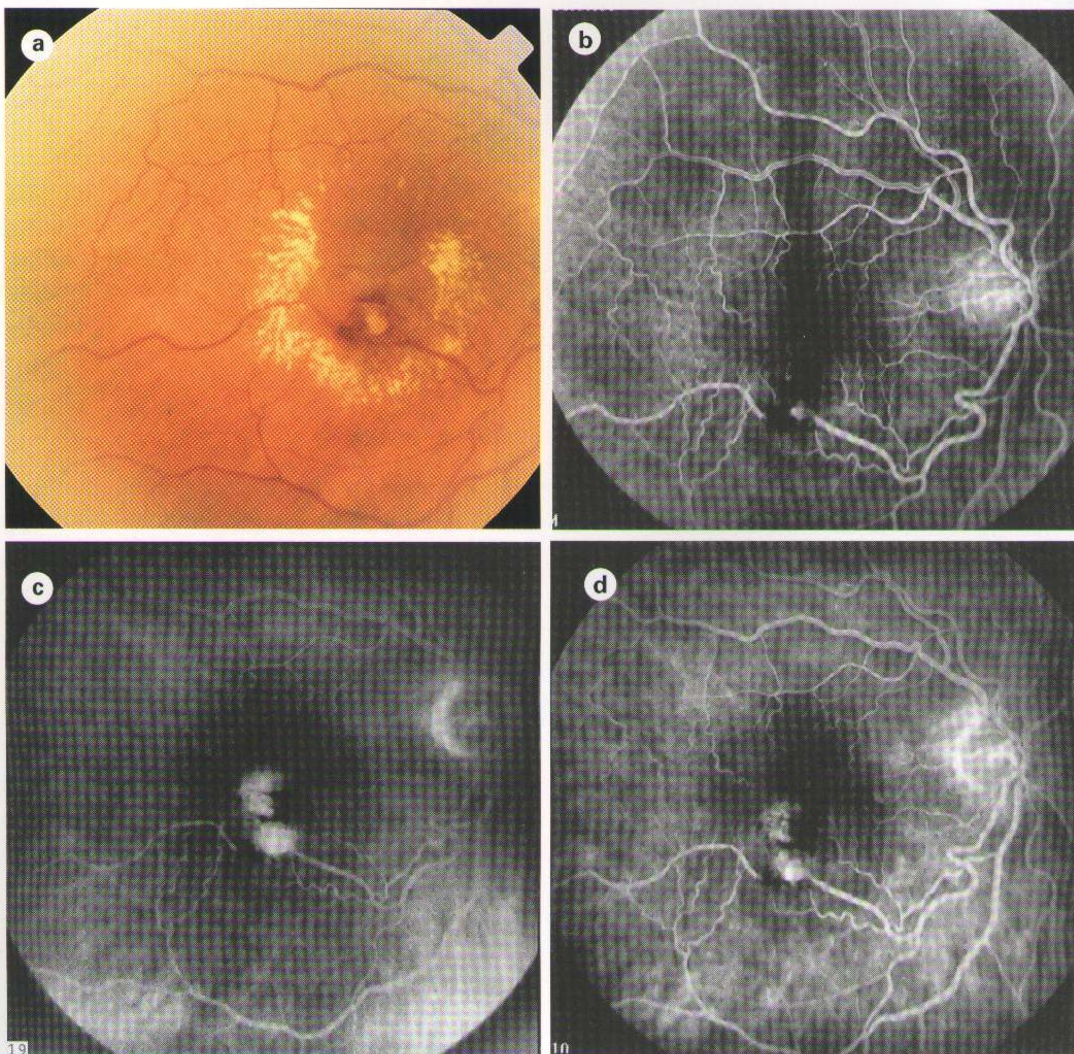


Fig. 14.108
(**a**) Leaking retinal artery macroaneurysm with a small haemorrhage and surrounding hard exudates; (**b**) early venous phase FA showing filling; (**c**) late venous phase showing late leakage; (**d**) late phase showing further leakage (Courtesy of S. Milewski)

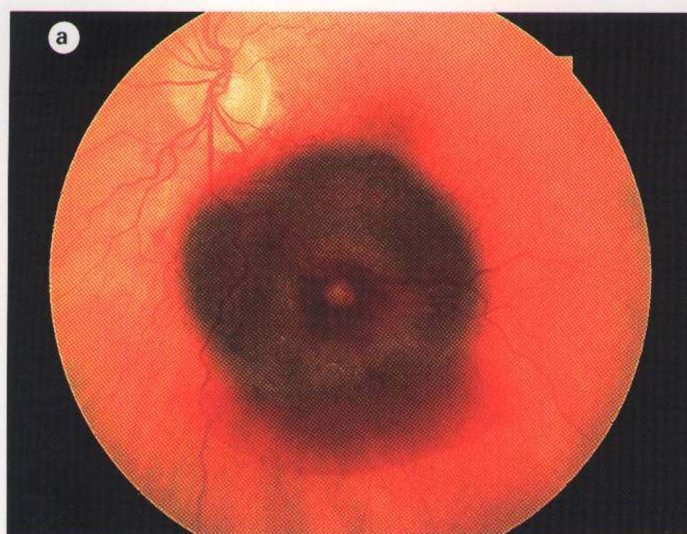
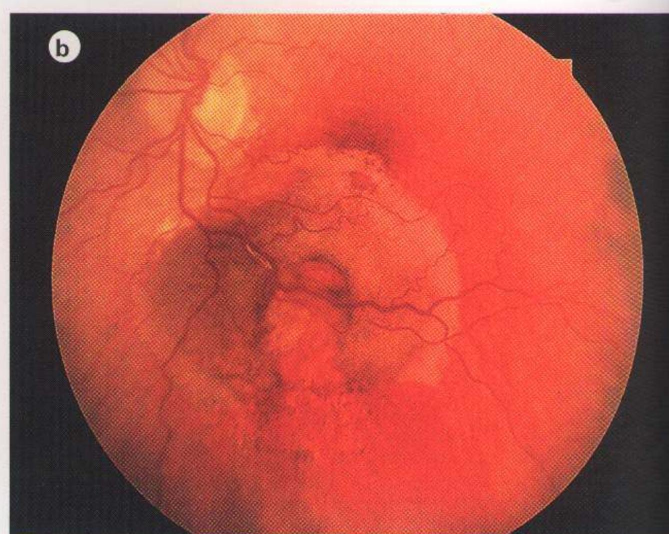



Fig. 14.109
(a) Subretinal haemorrhage associated with retinal artery macroaneurysm; **(b)** following spontaneous involution and absorption of blood

shallowing of the anterior chamber caused by a forward movement of the iris–lens diaphragm and the development of anterior synechiae. Treatment is by lensectomy and anterior vitrectomy.

Retinal artery macroaneurysm

A retinal artery macroaneurysm is a localized dilatation of a retinal arteriole which usually occurs in the first three orders of the arterial tree. It has a predilection for elderly hypertensive women and involves one eye in 90% of cases.

Clinical features

1. **Presentation** may be in one of the following ways:
   - Detection by chance of an asymptomatic lesion.
   - Insidious impairment of central vision due to macular oedema and hard exudate formation.
   - Sudden visual loss resulting from vitreous haemorrhage is uncommon.
2. **Fundus**
   - A saccular or fusiform arteriolar dilatation, most frequently occurring at a bifurcation or an arteriovenous crossing along the temporal vascular arcades. The aneurysm may enlarge to several times the diameter of the artery.
   - Associated retinal haemorrhage is present in 50% of cases (Fig. 14.107).
   - Multiple macroaneurysms along the same or different arterioles may be present.
3. **FA** findings are dependent on the patency of the lesion and any associated haemorrhage. The typical appearance is that of early uniform filling of the macroaneurysm (Fig. 14.108b) with late leakage (Fig. 14.108c and d). Incomplete filling is due to partial or complete obliteration of the lumen by thrombosis.
4. **Course**
   - Spontaneous involution following thrombosis and fibrosis is very common. This may precede or follow the development of leakage or haemorrhage (Fig. 14.109).
   - Rupture with haemorrhage (Fig. 14.110), which may be subretinal, intraretinal, preretinal or vitreous. In these cases the underlying lesion may be overlooked and the diagnosis missed.
   - Chronic leakage resulting in retinal oedema with accumulation of hard exudates at the fovea is common and may result in permanent loss of central vision (*see* Fig. 14.108a).

Management

1. **Observation** in anticipation of spontaneous involution is indicated in eyes with good visual acuity in which

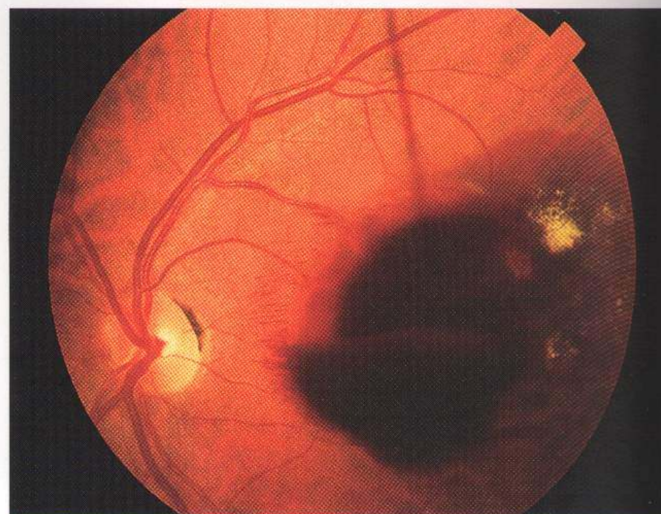


Fig. 14.110
Subretinal and preretinal haemorrhage associated with a retinal artery macroaneurysm (Courtesy of S. Milewski)

the macula is not threatened and those with mild retinal haemorrhage without significant oedema or exudation.

2. **Argon laser photocoagulation** may be considered if oedema or hard exudates threaten or involve the fovea (Fig. 14.111a), particularly if there is documented visual deterioration. The burns may be applied to the lesion itself, the surrounding area, or both (Fig. 14.111b). It may take several months for the oedema and hard exudates to absorb.
3. **YAG-laser hyaloidotomy** may be considered in eyes with large non-absorbing preretinal haemorrhages overlying the macula in order to disperse the blood into the vitreous cavity, from where it may be absorbed more quickly.

Differential diagnosis

1. **Hard exudates at the posterior pole**
   - Background diabetic retinopathy.
   - Exudative age-related macular degeneration.
   - Old retinal branch vein occlusion.
   - Retinal telangiectasia.
   - Small retinal capillary haemangioma.
   - Radiation retinopathy.
2. **Deep retinal or subretinal haemorrhages at the posterior pole**
   - Choroidal neovascularization.
   - Valsalva retinopathy.
   - Idiopathic polypoidal choroidal vasculopathy.
   - Blunt ocular trauma.
   - Choroidal melanoma.
   - Terson syndrome associated with subarachnoid haemorrhage.

Primary retinal telangiectasia

The primary retinal telangiectasias are a group of rare, idiopathic, congenital or acquired, retinal vascular anomalies characterized by dilatation and tortuosity of retinal blood vessels, multiple aneurysms, vascular leakage and the deposition of hard exudates. Retinal telangiectasias involve the capillary bed, although the arterioles and venules may also be involved. The vascular malformations often progress and become symptomatic later in life as a result of haemorrhage, oedema or lipid exudation. Primary and secondary telangiectasias should be distinguished from each other, the latter being associated with an underlying systemic disease, such as diabetes. According to severity primary retinal telangiectasias can be divided into: (a) *idiopathic juxtafoveolar retinal telangiectasia*, (b) *Leber miliary aneurysms* and (c) *Coats disease*. Some authorities consider Leber miliary aneurysms to be a localized and milder form of Coats disease.

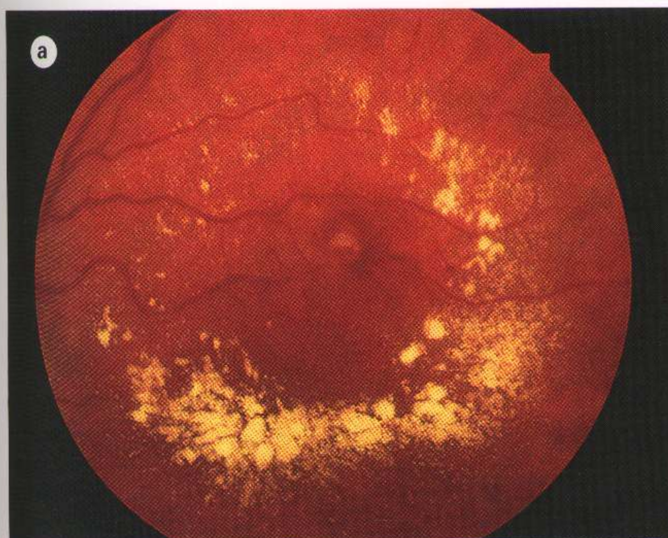
Idiopathic juxtafoveolar retinal telangiectasia

Idiopathic juxtafoveolar telangiectasia is a rare, congenital or acquired condition which can be divided into the following types.

Group 1A: unilateral parafoveal telangiectasia

This typically affects middle-aged men.

1. **Presentation** is with mild to moderate blurring of vision.



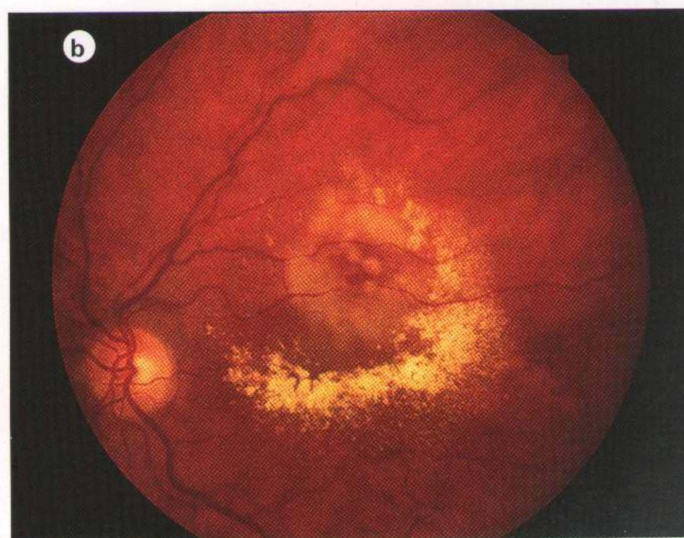


Fig. 14.111
(a) Leaking retinal artery macroaneurysm with hard exudates involving the fovea; (**b**) appearance immediately following laser photocoagulation

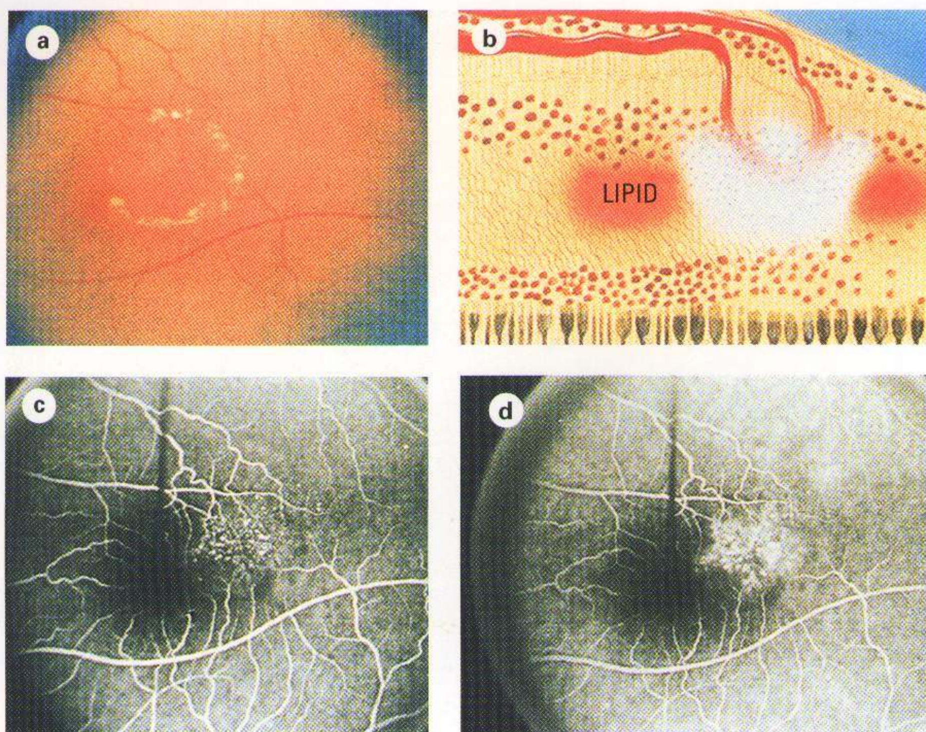


Fig. 14.112
Idiopathic juxtafoveolar retinal telangiectasia: group 1A (*see text*) (Courtesy of Wilmer Institute)

2. **Signs**. Telangiectasia, about 1.5 disc diameters in area, temporal to the fovea and frequently associated with hard exudates (Fig. 14.112a and b).
3. **FA** shows capillary dilatation (Fig. 14.112c) and late leakage (Fig. 14.112d).
4. **Treatment** by laser photocoagulation to areas of leakage may be beneficial in preventing visual loss.

Group 1B: unilateral parafoveal telangiectasia

This typically affects middle-aged men.

1. **Presentation** is with mild blurring of vision.
2. **Signs**. Telangiectasia confined to one clock hour at the edge of FAZ (Fig. 14.113a and b).
3. **FA** shows absence of leakage (Fig. 14.113c).
4. **Treatment** is not appropriate and the prognosis is good.

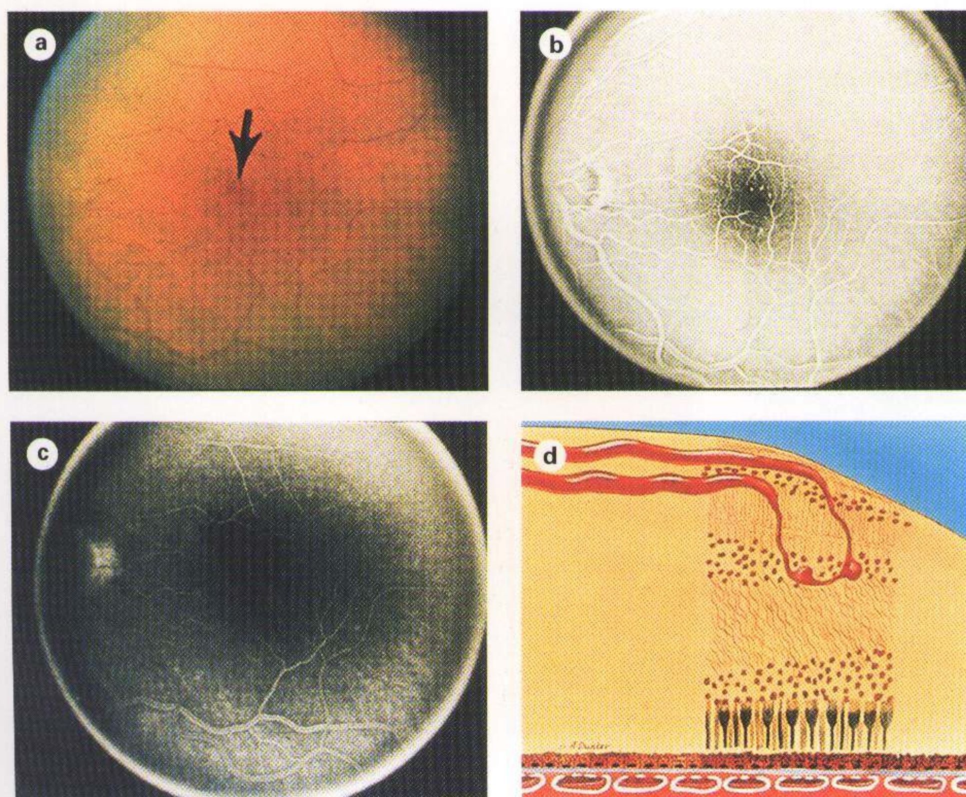


Fig. 14.113
Idiopathic juxtafoveolar retinal telangiectasia: group 1B (*see text*) (Courtesy of Wilmer Institute)

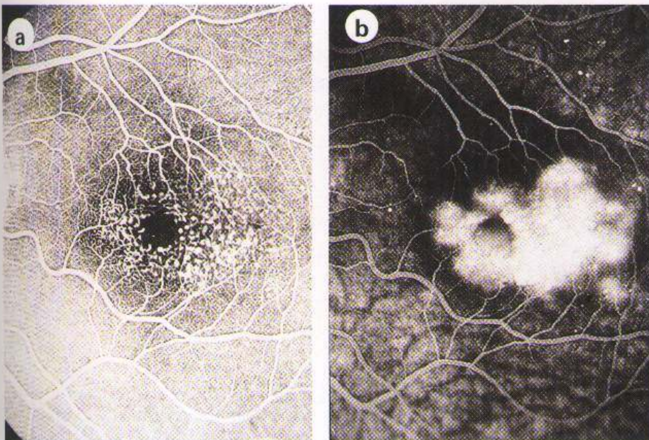


Fig. 14.114
Idiopathic juxtafoveolar retinal telangiectasia: group 2 (*see text*)

Group 2: bilateral parafoveolar telangiectasia

1. **Presentation** is in the fifth to sixth decades with mild, slowly progressive disturbance of central vision.
2. **Signs**
   - Symmetrical telangiectasia, one disc area or less, involving all or a part of the parafoveolar retina without hard exudates but frequently associated with stellate plaques of RPE hyperplasia.
   - Multiple glistening white juxtafoveolar dots and solitary small yellow central deposits may be present.
3. **FA** shows capillary dilatation outside the FAZ (Fig. 14.114a) and late leakage (Fig. 14.114b).
4. **Prognosis** is guarded because of the development of secondary foveal atrophy and occasionally CNV. Laser photocoagulation may be of benefit in patients with CNV but not otherwise.

Group 3: bilateral perifoveal telangiectasia and capillary occlusion

This is the most severe form and typically presents in the sixth decade.

1. **Presentation** is with slowly progressive loss of central vision.
2. **Signs**
   - Marked aneurysmal dilatation of terminal capillaries and progressive occlusion of perifoveal capillaries.
   - Optic atrophy may be present.
3. **FA** shows widening of FAZ but absence of leakage.
4. **Prognosis** is usually poor.

Leber miliary aneurysms

1. **Presentation** is in adult life with unilateral impairment of central vision.
2. **Signs**
   - Fusiform and saccular dilatation of venules and arterioles, most commonly involving the temporal retinal periphery (Fig. 14.115).

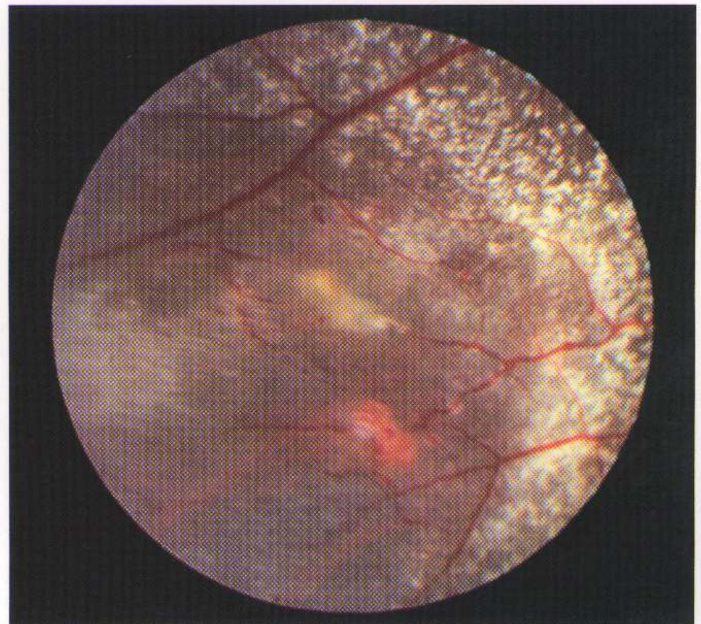


Fig. 14.115
Peripheral lesions in Leber miliary aneurysms

   - Chronic leakage results in intraretinal hard exudate formation which may involve the macula.
3. **FA** during the early phase highlights the vascular anomalies and shows areas of retinal non-perfusion (Fig. 14.116b). The late phase shows leakage (Fig. 14.116c).
4. **Prognosis** is dependent on the extent of foveal involvement by hard exudates at the time of diagnosis (Fig. 14.117a).
5. **Treatment** to ablate the vascular anomalies by photocoagulation may be beneficial if applied early (Fig. 14.117b).

Coats disease

Coats disease is the most severe form of retinal telangiectasia. It is usually unilateral, typically affects young boys and can cause severe visual loss from exudative retinal detachment.

Clinical features

1. **Presentation** is typically in the first decade (average 5 years) with visual loss, strabismus or a white fundus reflex (leukocoria) (Fig. 14.118).
2. **Signs** (in chronological order)
   - Retinal telangiectasia, most often in the inferior and temporal quadrants between the equator and ora serrata, and sometimes posterior to the equator towards the vascular arcades (Fig. 14.119).
   - Intraretinal and subretinal yellowish exudation (Figs 14.120 and 14.121a) often affecting areas remote from the vascular abnormalities, particularly the macula.

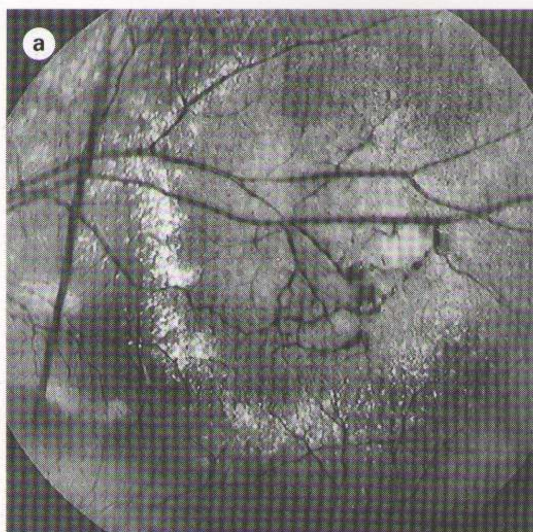
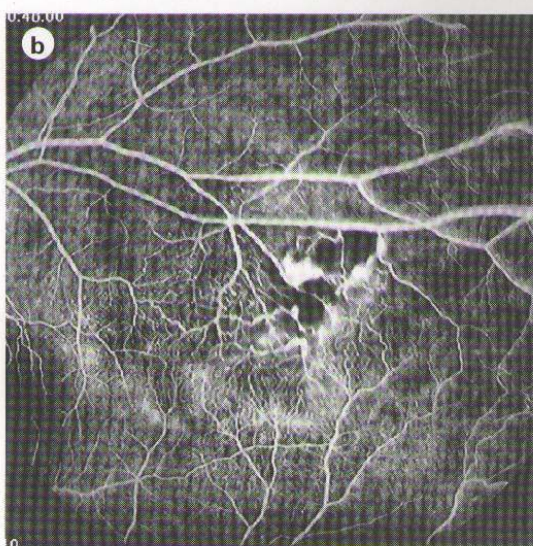
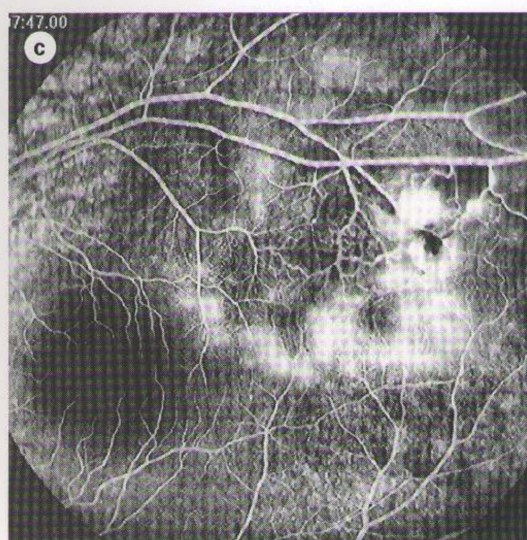
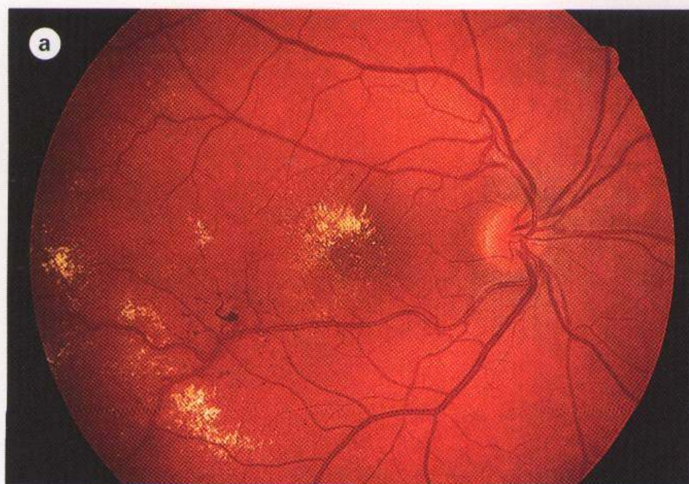


Fig. 14.116
(**a**) Red-free photograph of Leber miliary aneurysms; (**b**) FA showing focal venous dilatation and non-perfusion; (**c**) late FA showing leakage (Courtesy of S. Milewski)







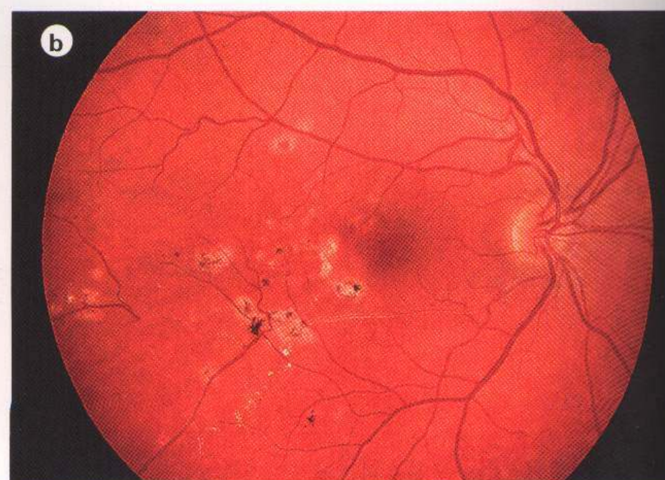


Fig. 14.117
(**a**) Hard exudates in Leber miliary aneurysms; (**b**) absorption of hard exudates following laser photocoagulation (Courtesy of S. Milewski)



Fig. 14.118
White pupil (leukocoria) in advanced Coats disease

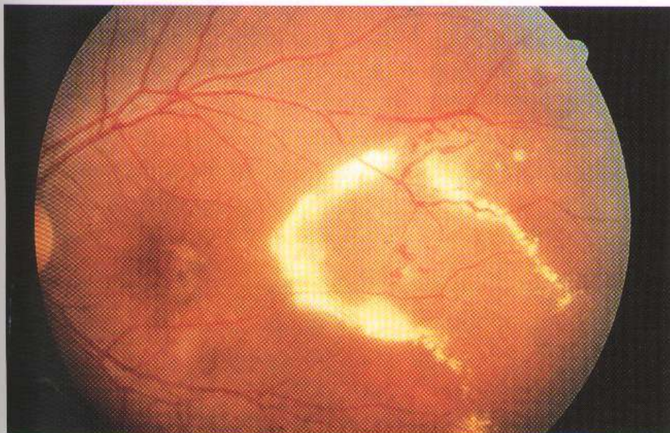


Fig. 14.119
Vascular changes and exudates in early Coats disease

3. **Complications** include exudative retinal detachment, rubeosis iridis, glaucoma, uveitis and phthisis bulbi.
4. **FA** highlights the underlying telangiectasia. Tortuosity, aneurysm formation and non-perfusion are seen with variable blockage of background choroidal fluorescence by hard exudates (Fig. 14.121b).
5. **Ultrasonography** in eyes with total retinal detachment is useful to exclude exophytic retinoblastoma.
6. **Differential diagnosis** includes other causes of unilateral leukocoria and retinal detachment in children such as late-onset retinoblastoma, toxocariasis, incontinentia pigmenti and retinal capillary haemangioma.

Management

1. **Observation** in patients with mild, non-vision-threatening disease and in those with a comfortable eye with total retinal detachment in which there is no hope of restoring useful vision.
2. **Photocoagulation** to areas of telangiectasia in eyes with exudation but no or very shallow retinal detachment.
3. **Cryotherapy**, with a double freeze–thaw method, when retinal detachment is shallow enough to allow approximation of the cryoprobe to the telangiectasia.
4. **Vitreoretinal surgery** in eyes with deep retinal detachments unsuitable for cryotherapy.

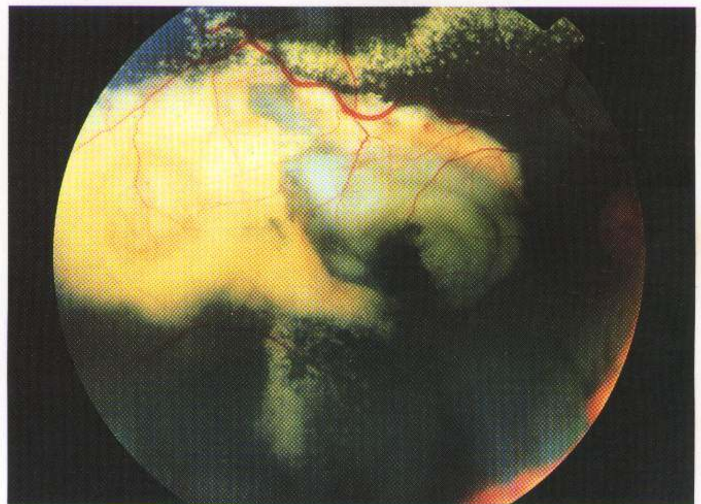
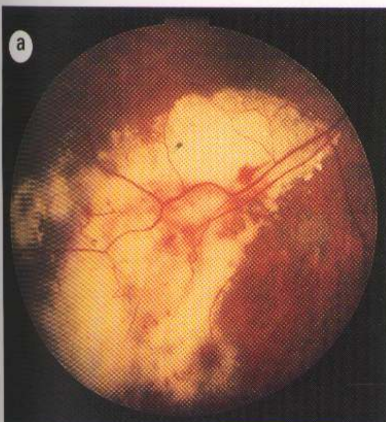


Fig. 14.120
Extensive subretinal exudation in advanced Coats disease



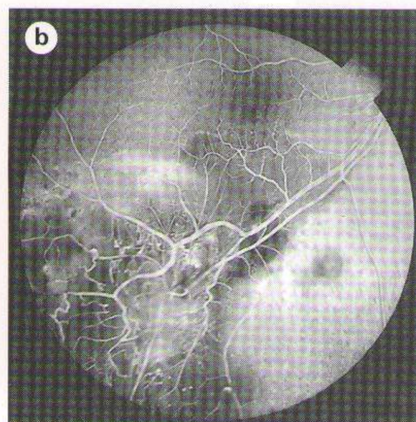


Fig. 14.121
(**a**) Coats disease; (**b**) FA showing vascular abnormalities and blockage of background fluorescence by hard exudates (Courtesy of S. Milewski)

Radiation retinopathy

Radiation retinopathy may develop following treatment of intraocular tumours by plaque therapy (brachytherapy) or external beam irradiation of sinus, orbital or nasopharyngeal malignancies.

1. **Presentation**. The time interval between exposure and disease is variable and unpredictable, although commonly between 6 months and 3 years.
2. **Signs** (in chronological order)
   - Discrete capillary occlusion with the development of collateral channels and microaneurysms, best seen on FA (Fig. 14.122).
   - Macular oedema, hard exudates and flame-shaped retinal haemorrhages (Fig. 14.123).
   - Papillopathy, widespread arteriolar occlusion and cotton wool spots.
   - Proliferative retinopathy and tractional retinal detachment.
3. **Treatment** by laser photocoagulation may be beneficial for macular oedema and proliferative retinopathy. Papillopathy is treated with systemic steroids.
4. **Prognosis** depends on the severity of involvement. Poor prognostic features include papillopathy and proliferative retinopathy, which may result in vitreous haemorrhage and tractional retinal detachment.

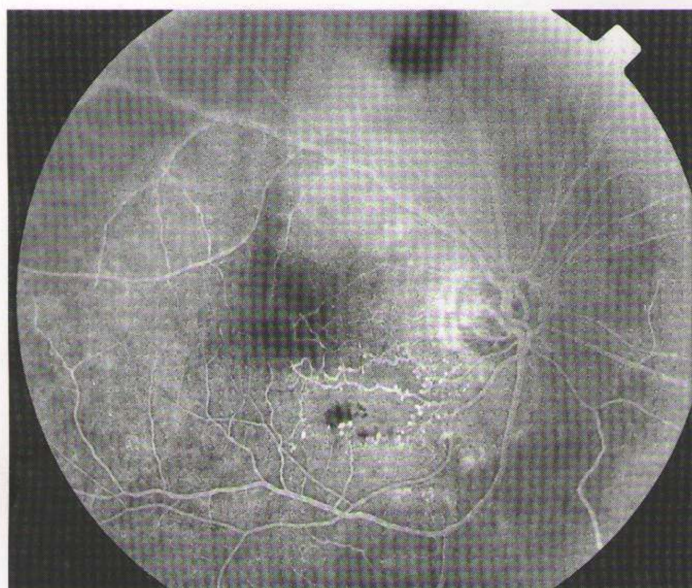


Fig. 14.122
FA of early radiation retinopathy showing focal retinal capillary non-perfusion associated with microvascular changes (Courtesy of S. Milewski)

Purtscher retinopathy

Purtscher retinopathy is caused by microvascular damage with occlusion and ischaemia associated with (a) *severe head trauma*, (b) *chest compression injury*, (c) *embolism* (fat, air or amniotic fluid) and (d) *systemic diseases* (acute pancreatitis, pancreatic carcinoma, connective tissue diseases, lymphomas, thrombotic thrombocytopenic purpura and following bone marrow transplantation).

1. **Signs**. Multiple, superficial, white retinal patches, resembling large cotton wool spots, often associated with superficial peripapillary haemorrhages (Fig. 14.124).
2. **FA** shows variable capillary non-perfusion and blockage of background choroidal fluorescence by haemorrhages and oedema.
3. **Treatment** of the underlying cause is desirable but not always possible.
4. **Prognosis** is guarded because although the acute fundus changes usually resolve within a few weeks permanent variable visual impairment occurs in approximately 50% of cases as a result of macular or optic nerve damage.

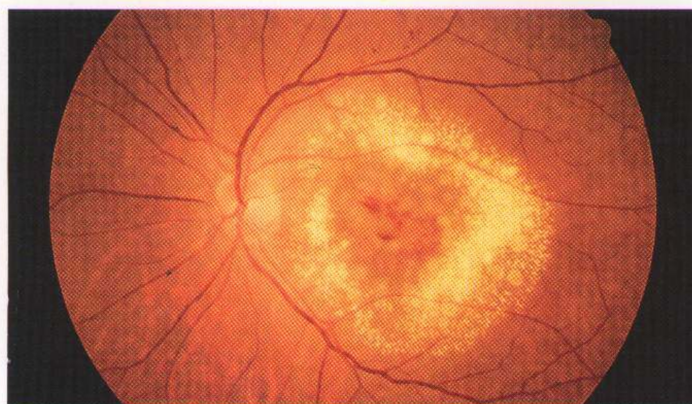


Fig. 14.123
Severe radiation retinopathy with macular oedema and hard exudates



Fig. 14.124
Purtscher retinopathy

Retinopathy in blood dyscrasias

Anaemia

The anaemias are a group of disorders characterized by a decrease in the number of circulating red blood cells, a decrease in the amount of haemoglobin in each cell, or both. Retinal changes in the anaemias are usually innocuous and rarely of diagnostic importance.

1. **Retinopathy** is characterized by haemorrhages, which may have white centres (Roth spots), cotton wool spots and venous tortuosity (Fig. 14.125).
   - The duration and type of anaemia do not influence the occurrence of these changes, which are more common with coexistent thrombocytopenia.
   - Flame-shaped haemorrhages and cotton wool spots may occur in the absence of other haematological abnormalities.
   - Retinal venous tortuosity appears related to the severity of anaemia.
   - Roth spots represent fibrin thrombi occluding ruptured blood vessels. They may also occur in bacterial endocarditis and leukaemia.
2. **Optic neuropathy** with centrocaecal scotomas may occur in patients with pernicious anaemia. Unless treated with vitamin B_{12} supplements, permanent optic atrophy may ensue. Pernicious anaemia may also cause dementia, peripheral neuropathy and subacute combined degeneration of the spinal cord characterized by posterior and lateral column disease.

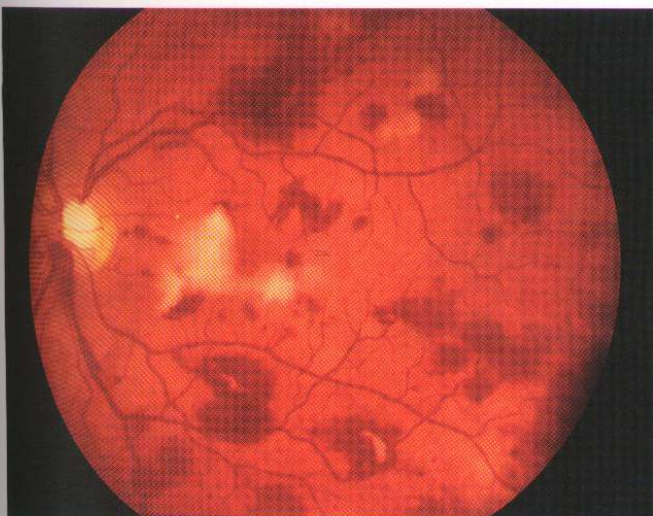


Fig. 14.125
Retinopathy in severe anaemia with Roth spots

Leukaemia

The leukaemias are a group of neoplastic disorders characterized by abnormal proliferation of white blood cells. Ocular involvement is more commonly seen in the acute than the chronic form and virtually any ocular structure may be involved. It is, however, important to distinguish the fairly rare primary leukaemic infiltration from the more common secondary changes such as those associated with anaemia, thrombocytopenia, hyperviscosity and opportunistic infections.

1. **Retinopathy** is relatively common. The findings are similar to those in anaemia with flame-shaped haemor-

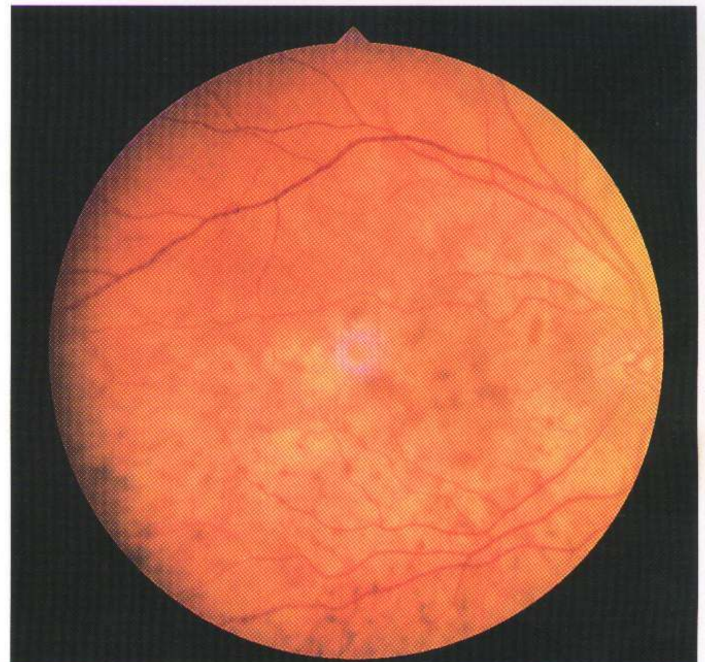


Fig. 14.126
'Leopard spot fundus' in chronic leukaemia

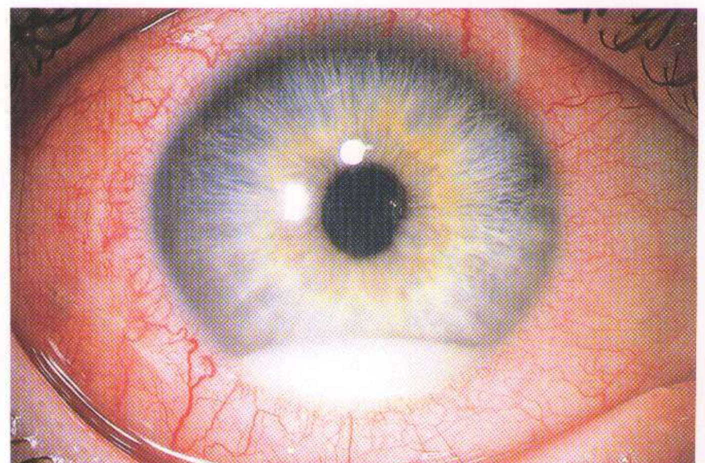


Fig. 14.127
Pseudo-hypopyon in acute leukaemia

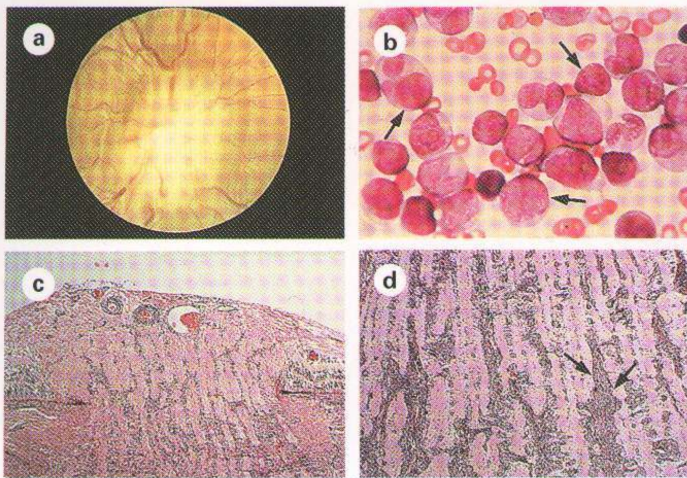


Fig. 14.128
Optic nerve infiltration in acute lymphocytic leukaemia. (**a**) Infiltration of the optic nerve head resulting in greyish-white elevation; (**b**) blood smear showing lymphoblasts; (**c**) disc elevation due to infiltration by leukaemic cells; (**d**) high-power section of retrolaminar optic nerve showing leukaemic infiltration (Courtesy of Wilmer Institute)

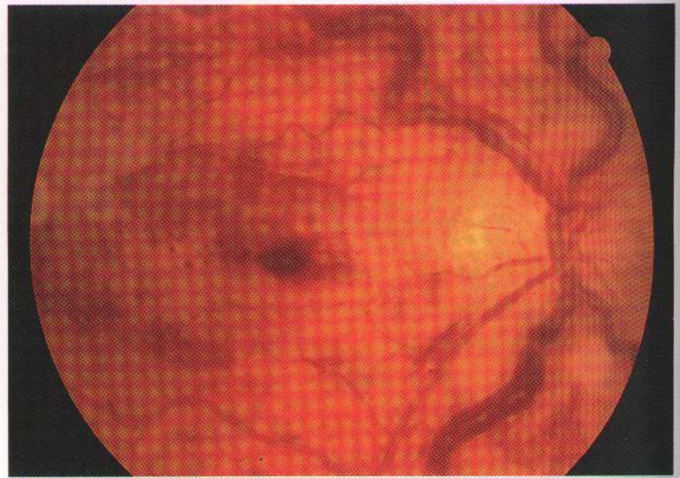


Fig. 14.129
Gross venous dilatation and haemorrhages in hyperviscosity

rhages, Roth spots and cotton wool spots. The latter may be the result of leukaemic infiltration or secondary to anaemia or hyperviscosity. Peripheral retinal neovascularization is an occasional feature of chronic myeloid leukaemia. Rarely, leukaemic pigment epitheliopathy, characterized by a 'leopard spot' fundus, may occur secondary to choroidal infiltration (Fig. 14.126).

2. **Other ocular features**
   - Orbital involvement, particularly in children (*see* Fig. 17.79).
   - Iris thickening, iritis and pseudo-hypopyon (Fig. 14.127).
   - Spontaneous subconjunctival haemorrhage and hyphaema.
   - Optic neuropathy due to infiltration of the optic nerve (Fig. 14.128).

Hyperviscosity states

The hyperviscosity states are a diverse group of rare disorders characterized by increased blood viscosity due to polycythaemia or abnormal plasma proteins as in Waldenström macroglobulinaemia and myeloma. Retinopathy is characterized by venous dilatation, segmentation and tortuosity, and retinal haemorrhages (Fig. 14.129).